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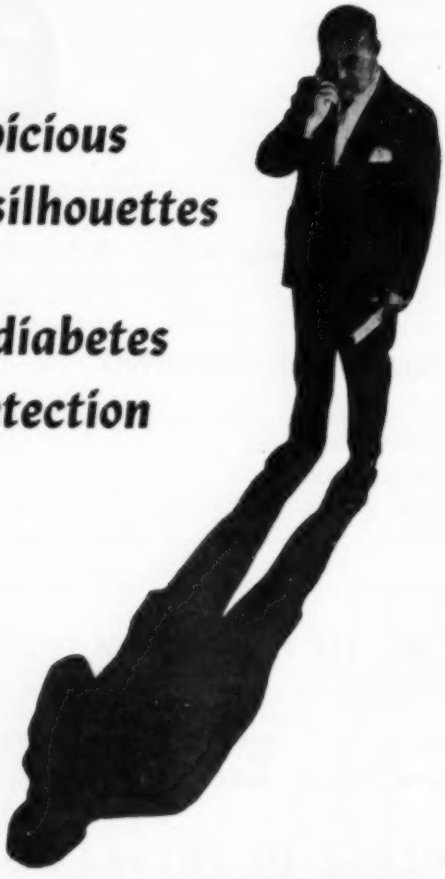
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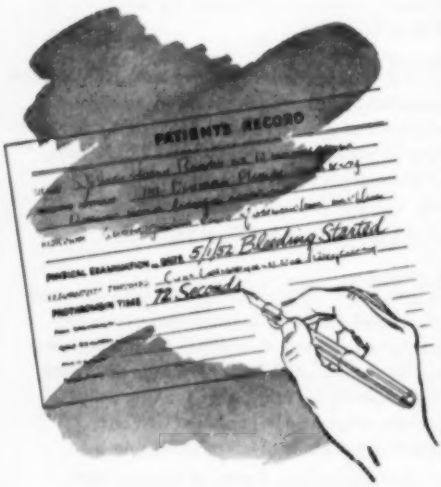
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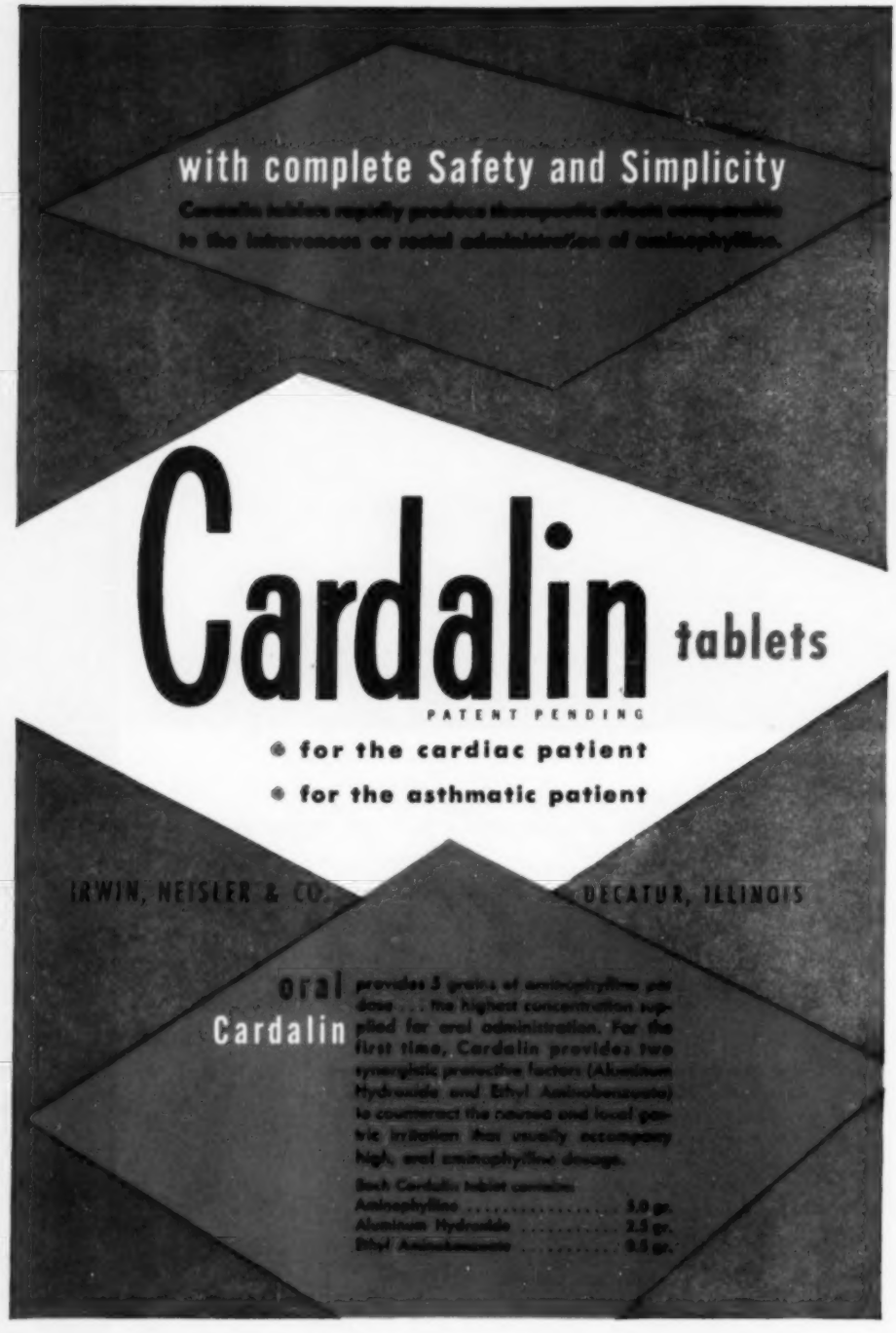
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*1. Humphreys, P., et al: Angiology 3:1 (Feb.) 1952. 2. Plotz, M.: New York State J. Med., 52:2012-2014 (Aug. 15) 1952. 3. Perlman, A.: Angiology 3:16 (Feb.) 1952. 4. Samuels, S.S., et al.: Angiology 3:30 (Feb.) 1952.*

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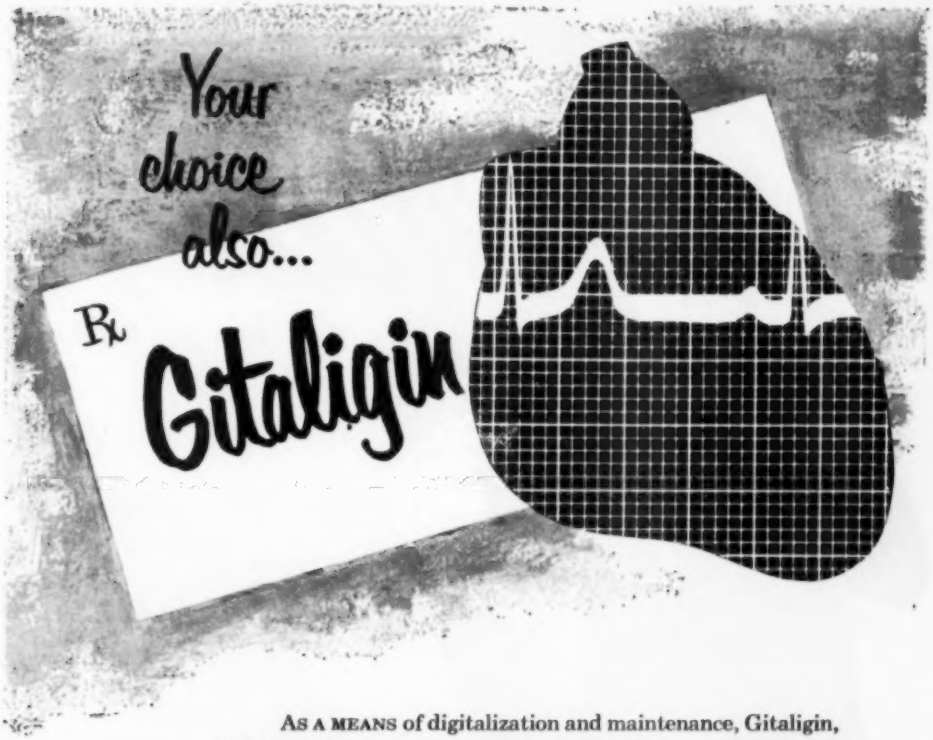
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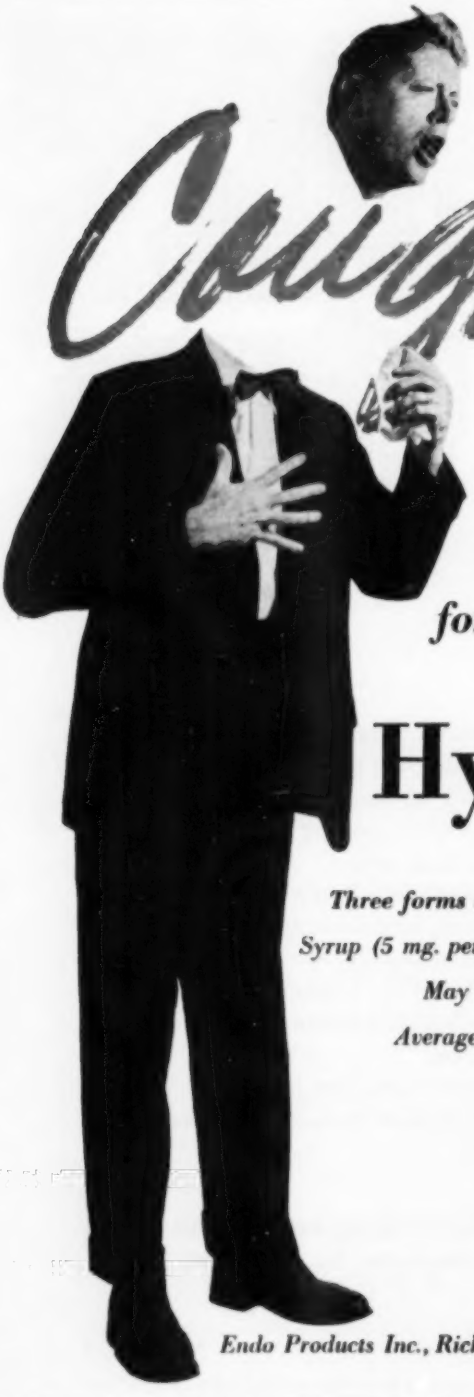
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1. Batterman, R. C.; DeGraff, A. C.; Gutner, L. B.; Rose, O. A., and Howe, J.: Studies with Gitalin (amorphous) for the Treatment of Patients with Congestive Heart Failure, Am. Heart J. **42**:292-307 (Aug.) 1951.

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3. Nalefski, L.: Personal Communication



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This is possible with AMINODROX because gastric disturbance is avoided.

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1. Steinbrocker, O.; Berkowitz, S.; Ehrlich, M.; Elkind, M., and Carp, S.: Paper read before the Annual Meeting of the American Rheumatism Association, Chicago, Ill., June 6, 1952.
2. Kusell, W. C.; Schaffarnick, R. W.; Brown, B., and Mankle, E. A.: J.A.M.A. *149*:729 (June 21) 1952.
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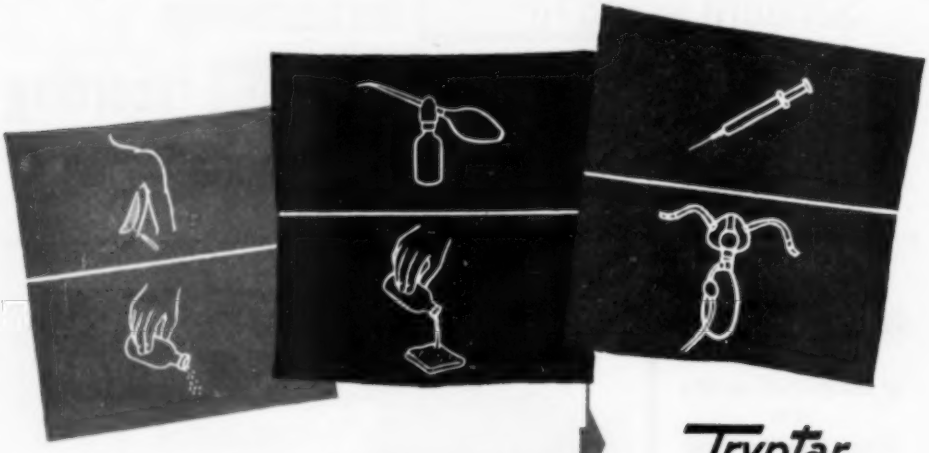
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PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH

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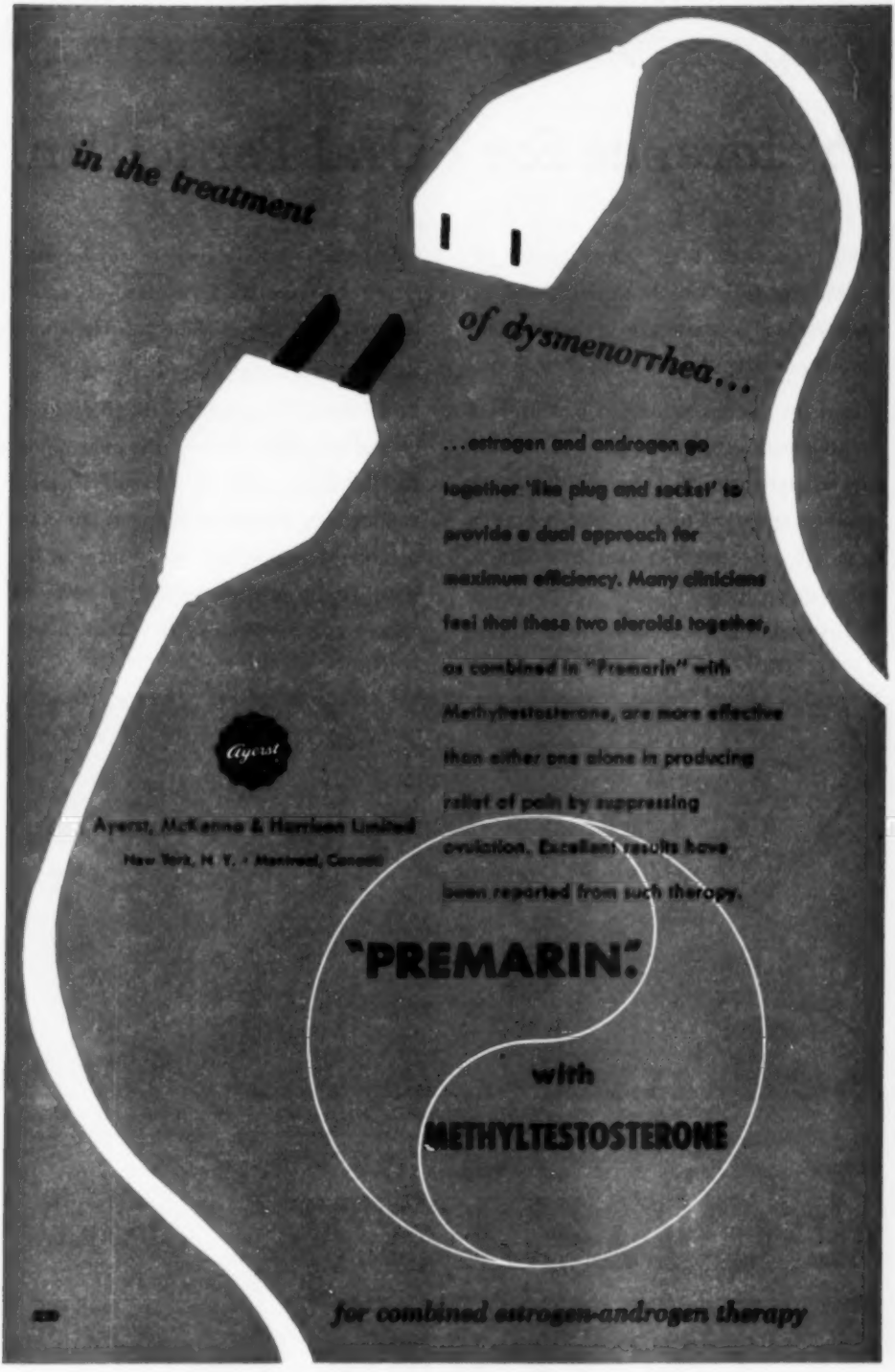
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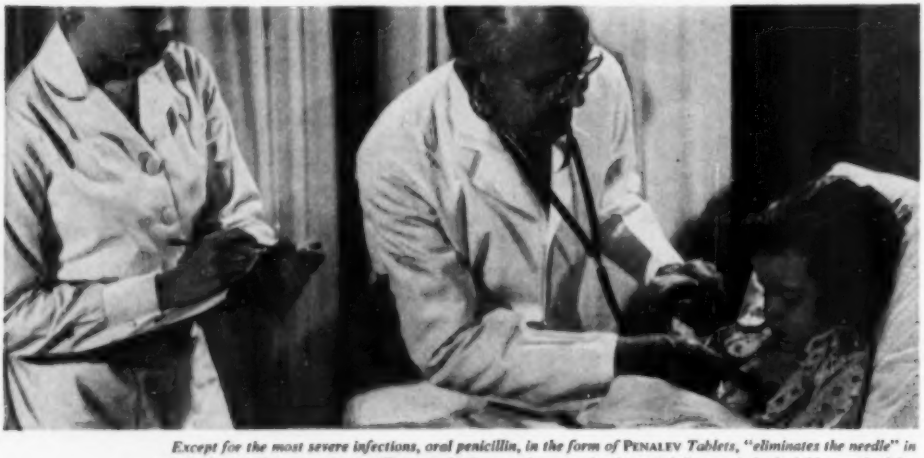
# Preference for Oral Penicillin

A highlight of the 101st Annual Session of the Medical Society of the State of Pennsylvania was a panel discussion of the more important new drugs used in internal medicine.

Initially, the discussion centered around the treatment of bacterial pneumonia with various antibacterials. One of the panel members remarked that "we give penicillin by mouth . . . we prefer to give it by mouth."[1] Other panel members were in agreement that penicillin is the drug of choice. "The temperature responses in the various groups (given other, costlier antibiotics)—illustrate the point that oral penicillin is as effective ..."[1]

*Less Sensitivity With Oral Penicillin?*

There is now no question of the effectiveness of oral penicillin except in the most refractory infections, such as subacute bacterial endocarditis. Furthermore, many clinicians are of the impression that, "there is less sensitivity to penicillin when it is given by mouth . . . than by the hypodermic method."[1]



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1. Panel Discussion, Pennsylvania M.J., 55:42, Jan., 1952.

ANNALS OF
INTERNAL MEDICINE

VOLUME 38 JANUARY, 1953 NUMBER 1

# FOLLOW-UP STUDIES ON THE FIRST 1,000 PATIENTS OPERATED ON FOR PULMONARY STENOSIS OR ATRESIA (RESULTS UP TO MARCH, 1952) *

By HELEN B. TAUSSIG, M.D., and S. RICHARD BAUERSFELD, M.D.,
*Baltimore, Maryland*

THIS report is concerned with the first 1,000 patients operated upon by Dr. Alfred Blalock and his associates for the alleviation of pulmonary stenosis or atresia by a systemic-pulmonic anastomosis. These patients were operated upon between November, 1944, and October, 1950, and have been followed up to March 1, 1952; hence, all of these patients have been followed for at least 18 months and some for more than seven years.

As in the previous report,[1] the results are classified as good, fair, unimproved and died. A *good* result means that, regardless of the degree of incapacity before operation, cyanosis was markedly decreased, the oxygen saturation of the arterial blood rose to between 75 per cent and 90 per cent; in most instances the red blood cell count, the amount of available hemoglobin and the hematocrit reading returned to approximately normal values and there was marked subjective improvement. A *fair* result means that the patient was improved by operation but that cyanosis and polycythemia of varying degrees persisted. The group of patients *unimproved* by operation not only includes those who derived no benefit from operation but also those in whom it was technically impossible to complete the operation. As previously reported, 773 patients obtained good results from operation, 39 obtained fair results, 31 were unimproved and 157 patients died at or immediately after operation.† Thus the immediate mortality rate for the first

* This paper was presented at the Annual Meeting of the American College of Physicians in Cleveland, April, 1952, and has been recently published in a Festschrift volume for Dr. Gustav Nylin in Sweden.

† The slight discrepancy between these figures and those reported a year ago is due to the fact that in the analyses of 1,000 patients by different individuals it is inevitable that a few errors crept in. These we have tried to eliminate.

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1,000 consecutive patients operated on for pulmonary stenosis or atresia was 15.7 per cent.

The above figures include patients with all types of malformations in which the outstanding feature was pulmonary stenosis or atresia and who we thought would be benefited by a systemic-pulmonic anastomosis. Prior to operation, 857 patients were diagnosed as tetralogy of Fallot; 62 patients had electrocardiographic evidence of left axis deviation or left ventricular hypertrophy and therefore were diagnosed as tricuspid atresia; 27 patients were diagnosed as pseudo-truncus arteriosus, either on the basis of a continuous murmur or because of the contour of the heart; 32 patients had evidence of dextrocardia or dextrorotation, and 11 were known to have situs inversus with levocardia. The remaining 11 patients were believed to suffer from lack of adequate pulmonary blood flow but the exact nature of the malformation was not certain. Six were believed to have a single ventricle. Three patients had valvular pulmonary stenosis with an intact ventricular

TABLE I

Result of Operation According to Type of Malformation

| Type Malformation | | T/F | Tric. Atre. | Trunc. Art. | Dex.-Car. | Situs Inv. and Lev. | Diag. Uncertain |
|---|---|---|---|---|---|---|---|
| No. Pts. | | 857 | 62 | 27 | 32 | 11 | 11 |
| Result | Good | 78% | 69% | 59% | 78% | 91% | 46% |
| | Fair | 4% | 10% | 4% | | 9% | 9% |
| | Unimp. | 3% | | 11% | | | 18% |
| | Died | 15% | 21% | 26% | 22% | | 27% |
| Total Mort. 8 mos. P.O. | | 17% | 26% | 26% | 25% | 18% | 27% |

septum, and in the other two the nature of the malformation was not known. As regards the three patients diagnosed as valvular pulmonary stenosis, two died at operation and autopsy confirmed the diagnosis; in the third the subsequent course indicates that the diagnosis was incorrect, but the exact nature of the malformation remains obscure.

The results of operation and the mortality rate in these various groups are shown in table 1. Both the immediate mortality rate and the over-all mortality rate at the end of the first eight months are given because, in our experience, if the malformation is such that the heart cannot adjust to the altered circulation, the vast majority of these patients either die from heart failure or show evidence of severe congestive failure within this period. Therefore, the mortality rate at the end of eight months is of greater significance than is the immediate mortality rate.

For patients in whom the preoperative diagnosis was tetralogy of Fallot, 78 per cent obtained a good result from operation and the immediate mor-

tality rate was 15 per cent. During the ensuing eight months 14 patients died; thus the over-all mortality rate at the end of the first eight months was 17 per cent. All of these 14 patients, however, did not die as a result of operation. One died of a streptococcus meningitis, one died at the time of a second operation and one died suddenly of unknown cause.

Although 43 of 62 patients with tricuspid atresia were greatly improved by operation, and six obtained fair results, 21 per cent died at or shortly after operation. One of the patients who had obtained a fair result was in severe cardiac failure six months after operation and died from heart failure six weeks thereafter; in addition, one who had obtained a good result from operation died of subacute bacterial endocarditis within this period. A third patient died from pneumonia but with no evidence of cardiac failure. Thus the over-all mortality rate was 26 per cent.

Among the 27 patients diagnosed as truncus arteriosus, only 59 per cent obtained good results, 4 per cent obtained some improvement, 11 per cent were unimproved and 26 per cent died. During the ensuing six months there were no deaths in the group.

Although 78 per cent of the 32 patients with dextrocardia or dextrorotation of the heart obtained good results from operation, 22 per cent died at or shortly after operation, and an additional 3 per cent died from heart failure within the first eight months.

In the small group of patients with situs inversus and levocardia, 91 per cent obtained good results and 9 per cent fair results. Nevertheless, at the end of the first eight months two patients had died of congestive failure; consequently, the mortality rate had risen to 18 per cent.

Among the patients in whom the diagnosis was unknown, five had a good result, one a fair result, two were unimproved and three died at operation. Two of them, as previously mentioned, proved to have pure pulmonary stenosis and one had a defective development of the right ventricle and no right coronary artery.

The figures demonstrate that the results of operation are better and the risk of operation is less for patients with tetralogy of Fallot than for any of the other malformations. Further, in the group of atypical malformations all but two of the deaths during the first eight months after operation were due to cardiac failure, whereas among the 14 patients with tetralogy of Fallot who died during this period, only two were reported to have died of cardiac failure. In neither instance was autopsy obtained, and therefore it was impossible to tell whether in these two instances the diagnosis of tetralogy of Fallot was correct. The exact cause of death in the other patients is not known, but death was not believed to be due to congestive failure. Be that as it may, the low mortality rate in this period indicates that the vast majority of patients with tetralogy of Fallot are able to adjust to the altered circulation.

The mortality rate in this report, as in the previous one, has been analyzed on the basis of the preoperative diagnosis, because the possibility of an error

in diagnosis is a risk which every patient must take. In this series there have been 40 errors in diagnosis. In 33 instances autopsy revealed that the diagnosis had been grossly incorrect. In 13 instances we mistook a complete transposition of the great vessels for a tetralogy of Fallot; seven of these 13 patients, however, had pulmonary stenosis. The next most common error was to mistake a single ventricle with a pulmonary stenosis for a tetralogy of Fallot. There were seven patients who died at or shortly after operation in each of whom autopsy showed but a single ventricle. In four other patients, the aorta and the pulmonary artery both arose from the right ventricle; and in two instances there was a ventricular septal defect but no overriding of the aorta. One patient had an Ebstein's anomaly of the tricuspid valve, four had a pseudo-truncus arteriosus,* one had a "pure" pulmonary stenosis combined with a markedly underdeveloped right ventricle, and one had situs inversus and levocardia. All but four of these 33 patients died at or shortly after operation.

There remain seven other patients who were erroneously diagnosed as tetralogy of Fallot. One of these patients, upon reëvaluation and cardiac catheterization, was thought to have a single ventricle with pulmonary stenosis. Five of these remaining six patients proved to have valvular pulmonary stenosis with an intact ventricular septum. Although these patients survived operation and in each instance cyanosis was decreased, all five developed right sided cardiac failure. Four have subsequently had a Brock valvulotomy performed: one was greatly improved, three died at the second operation, and the fifth patient died in heart failure with subacute bacterial endocarditis. The fact that all five patients developed cardiac failure following a Blalock-Taussig operation clearly shows that patients with valvular pulmonary stenosis and no ventricular septal defect should have a Brock valvulotomy. Finally there remains one patient who was erroneously diagnosed as a pure pulmonary stenosis who, following unsuccessful valvulotomy, subsequently had a subclavian end-to-side anastomosis with a good result.†

In addition to the above mentioned patients, there were 15 patients in whom, although the diagnosis was technically correct, the aorta over-rode the ventricular septum by more than 50 per cent. All 15 patients died at or shortly after operation from acute pulmonary edema or severe pulmonary congestion. It is clear that too great over-riding of the aorta causes difficulty in the expulsion of blood from the left ventricle and leads to pulmonary congestion or acute pulmonary edema. Unfortunately, the extent to which the aorta over-rides the ventricular septum is one of the most difficult of the diagnostic problems. To date neither angiocardiography nor cardiac ca-

* These four patients were diagnosed as tetralogy of Fallot with persistent patency of the ductus arteriosus. Each proved at autopsy to have pseudotruncus arteriosus. We realize now that these findings are characteristic of a truncus arteriosus and have included them in the truncus group in order to give a true picture of the risk of operation in that malformation.

† This patient is not considered as "second operation" because it was her first Blalock-Taussig operation.

theterization has given reliable information. It remains as one of the "risks of operation" and one of the major causes of death in the early postoperative period. It also remains to be seen whether this group could be helped by a Brock valvulotomy, or whether such an operation would transform the malformation into an Eisenmenger complex.

Although inevitably we have not been able to keep in touch with every single patient, we have obtained follow-up information on 795 of the 843 patients who survived operation. To the best of our knowledge, 53 patients have died since discharge from the hospital. Of the remaining, 584 patients have had one or more postoperative examinations. Our information on 158 patients is based upon physicians' or parents' replies to our questionnaires. There remain only 48 patients (i.e., slightly less than 6 per cent) from whom we have received no information since discharge from the hospital. Therefore we believe the following figures give a reasonably true picture.

Let us first analyze the information obtained from the principal group, namely, those diagnosed as tetralogy of Fallot, then consider the long-time results in the atypical group, and finally review the incidence of subacute bacterial endocarditis in the entire series.

There were 730 patients who were diagnosed as tetralogy of Fallot who survived operation. Six hundred seventy-four of the patients obtained a good result from operation; 30 obtained a fair result and 26 derived no benefit from the operation. In this entire group, 43 patients have died and 114 failed to maintain their improvement. The 43 deaths include the 14 patients previously mentioned who died within the first eight months and nine patients who were unimproved by operation. Thus there were 34 late deaths among the patients improved by operation. Twenty-five of these deaths occurred among the 674 patients who obtained good results from operation, and nine deaths occurred among the 30 patients who obtained only fair results.

Hence, among those who obtained a good result from operation the mortality rate has been approximately 4 per cent, whereas among those who obtained a fair result it was 30 per cent, and among those unimproved by operation it was 35 per cent. Seven of these late deaths among those improved by operation occurred at the time of the second operation and will be discussed presently. It is furthermore worthy of note that the 25 late deaths among the patients who obtained a good result from operation include a number of deaths which are not attributable to the tetralogy of Fallot. One patient, as previously mentioned, died of a streptococcus meningitis, one died of leukemia and one was killed in an automobile accident, and in a number of instances our original diagnosis proved to be wrong. Three patients proved to have complete transposition of the great vessels with pulmonary stenosis, and three, as previously mentioned, had valvular pulmonary stenosis and intact ventricular septum and died at the time of a Brock valvulotomy. Therefore it is clear that the vast majority of patients with tetralogy of Fallot are able to adjust to the altered circulation.

Next let us consider those who have failed to maintain improvement. This group, of course, does not include those unimproved by operation. The group is composed of 674 patients who obtained good results and 30 who obtained fair results. Out of this entire group of 704 patients, 27 have died and 87 have failed to maintain the improvement derived from operation. Of these 87 patients, 28 have had a second operation, and the remaining 59 patients now show varying degrees of cyanosis and dyspnea. Certainly a second operation is indicated for a number of these patients.

When we consider second operations and the results therefrom, it must be remembered that a second operation is performed for a variety of reasons. A second operation has been attempted because the first operation was unsuccessful; it has also been attempted because the original diagnosis was wrong, and, finally, it has been performed because the patient failed to maintain the improvement derived from operation. Altogether there have been 40 second operations. Twenty-eight of these patients had been helped by the first operation, and the other 12 were among the small group of those unimproved by operation. In the latter group, eight obtained a good result from the second operation and four died. Of the four who died, two proved to have typical tetralogy of Fallot and two were among our errors of diagnosis and have previously been discussed as such.

Among the 28 patients who were helped by their first operation, 16 obtained good results from the second operation, four fair results, one was unimproved and seven died. All of these deaths have been included in our previous discussion. The high mortality rate in this group is explicable as follows: One of the deaths was that of our first patient, an infant under two years of age; three patients had their second operation performed elsewhere, and three of the deaths were among our original errors of diagnosis, i.e., they were the patients with "pure" pulmonary stenosis who died at the time of a Brock valvulotomy. Nevertheless, the fact remains that second operations carry a high mortality rate, thus emphasizing the importance of accurate diagnosis prior to cardiac surgery.

Now let us turn our attention to the atypical malformations. The results in this group are somewhat less favorable but are of the same general order. Of the 113 patients who survived surgery, 99 obtained a good result, nine a fair result and five were unimproved. In this group there have been 10 late deaths. Six of these have died eight months or less after operation. Six of these deaths were among those who obtained good results and four were among the nine who obtained fair results. Thus in the former group the mortality rate was 6 per cent and in the latter group 45 per cent. It so happens that all of the five patients unimproved by operation are still living.

Thus an analysis of both groups demonstrates that a good result from operation carries a far better prognosis than a fair result. Indeed, the prognosis in the latter group is only slightly better than among those un-

improved by operation. Nevertheless, if we consider the entire group of 704 patients with tetralogy of Fallot who were improved by operation, there are 34 patients who have died and 80 who failed to maintain the improvement, of whom 21 have survived a second operation. Thus 114 patients have not done well. Sixteen of these have obtained a good result from a second operation. This figure is less than 2 per cent higher than in our previous report.

We now have but 5 per cent from whom we have not heard, in contrast to the 7 per cent reported in 1951. Hence this means that less than 1 per cent have lost ground during the past year. In other words, 78 per cent of the entire group are still doing well.

The incidence of subacute bacterial endocarditis remains low. During the past two years we have learned of four additional cases of subacute bacterial endocarditis. Three were reported to us by physicians and one by the parents. The first three have been reported to be cured, and we do not know whether the fourth is authentic. Thus to the best of our knowledge there have been 22 cases of bacterial endocarditis and four deaths, two in the early postoperative period and two in the late. One child had and was cured of subacute bacterial endocarditis prior to operation. Eleven developed acute or subacute bacterial endocarditis in the early postoperative period, and 10 developed subacute bacterial endocarditis between two months and seven years after operation. Since no new patients have been added to the group, all four additional cases inevitably occurred in the late postoperative period. This does not, however, invalidate our opinion that in the early postoperative period these patients are extremely susceptible to subacute bacterial endocarditis and should receive large doses of prophylactic penicillin. Furthermore, the incidence of four cases of subacute bacterial endocarditis in a group of 790 patients observed for a year is an incidence of approximately one-half of 1 per cent, which is not much higher than is to be expected from any other group of patients with congenital malformations of the heart observed for a similar length of time. For this reason we believe the additional anomaly does not seriously increase the patient's susceptibility to subacute bacterial endocarditis.

## Summary

The results of the first 1,000 operations have been analyzed on the basis of those with tetralogy of Fallot and those with atypical malformations. The long-time results have been analyzed according to whether the patient obtained a good or a fair result or was unimproved by operation. Those who obtained a good result have done far better than those who obtained a fair result. Errors in original diagnosis are discussed. In the entire series there have been 53 late deaths, 43 in the group of patients with tetralogy of Fallot, and 10 among those with atypical malformations. The mortality rate has been significantly lower among those who obtained a good result

than in the other two groups. One hundred fourteen patients have failed to maintain improvement; 28 of these have had a second operation, and the others are still pending. During the seven-year period since the first operation there have been but 22 cases of subacute bacterial endocarditis, with four deaths.

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# IATROGENIC HEART DISEASE*

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## INTRODUCTION

IATROGENIC means "caused by a physician." Iatrogenic heart disease is an illness in which symptoms referable to the heart, or symptoms interpreted by the patient as such, are produced as a result of the words or actions of a physician. It is of importance for the following reasons: (1) The disease produces considerable morbidity and may easily be more disabling than the average case of organic heart disease; (2) the disease should be and is preventable; and (3) the treatment of the disease is specific and differs from the management of any other type of cardiac disorder.

The attention it has received is inadequate, there being only one reference by this title in the Index Medicus,[1] and no others, to my knowledge, using synonymous terminology. No textbook carries a chapter on iatrogenic heart disease, nor does the American Heart Association list iatrogeny in its etiologic classification.[2] It is true that the ease of production of a cardiac neurosis by the physician has been frequently mentioned.[1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12] The references, however, have almost invariably been oblique rather than direct, being included usually as part of a discussion of psychogenic cardiac disturbances in general. Similarly, in the American Heart Association classification, iatrogenic heart disease is expected to be listed under either effort syndrome (neurocirculatory asthenia), psychoneurosis, or both.[2] But iatrogenic heart disease has significant characteristics warranting its separation and especial emphasis. First, the etiology is distinct as set by definition. While some patients may have deep-seated personality disorders, the precipitating factor in all cases is the action of the physician, and many times this is the sole factor. Second, and as a natural corollary, therapy is ordinarily directed on a superficial plane, psychiatrically speaking, with emphasis on encouragement and reassurance rather than on deep psychologic probing. Third, and most important, separation of the disease points up the responsibility of the physician in its production, and gives hope that the physician so forewarned will be less likely to produce the disease in the future.

There are no statistics to my knowledge to indicate the frequency of this condition, but there are several reports suggesting its magnitude and importance. Writing on "Cardiac Neuroses," Oille [7a] stated: "Almost 60 per cent of patients who consult a cardiac specialist are suffering either from an exaggerated or wholly unnecessary anxiety about their hearts, arising from suggestion and not based on reason. . . . Most of the suggestions arise from

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the careless or ill-considered remarks of doctors." In a classic paper on "The Psychic Factor in Cardiac Disorders," Conner [4] featured the iatrogenic etiology as the first and foremost of the four factors which may produce a cardiac neurosis. Friedman [12] states in his monograph on "Functional Cardiovascular Disease" that, "Unfortunately at least 10 per cent of the hundreds of cases seen by the author were either caused or 'fixed' by some physician." One of the finest studies made on the condition labeled by the American Heart Association as "effort syndrome (neurocirculatory asthenia)" was reported by Wood [11] in 1941 under the designation "Da Costa's syndrome." He concluded that this is invariably a psychiatric illness, though often overlaid on other predisposing factors, such as family history, constitutional factors or debilitating illness. Wood made a detailed study of 100 unselected cases and reported that "Da Costa's syndrome may be induced by the doctor or by some other person in authority or it may be self-induced. The doctor was responsible in 17 cases and was an important factor in 16 others." It is evident from these references that iatrogenic heart disease is of considerable importance in clinical practice. It is also evident from the titles that this disorder is being submerged in larger categories, whereas it should be singled out for especial attention.

The most recent report was from the Work Classification Unit in New York, where persons were referred because of employment difficulties attributed to heart disease.[5] It is amazing that, out of 631 individuals who were adequately studied, 175 (or 28 per cent) were found to have no heart disease at all. The authors point out that iatrogenicity was a major factor in the disability of a substantial number of these patients.

## Pathogenesis

The pathogenesis of iatrogenic heart disease is quite clear. By definition, the etiologic agent is the physician. From him the patient receives the impression that he has heart disease. This may occur through direct statements or acts to that effect, or indirectly by the patient's interpretation of certain words or acts of the physician. It is a well known fact that the common reaction of the patient on receiving a diagnosis of heart disease is fear. Individuals vary in their responses, depending upon their personal makeup, their life experience and their situational reactions. But the general tendency of fear is to produce the combination of psychologic and physiologic manifestations commonly termed "anxiety neurosis" or "neurocirculatory asthenia." Unfortunately, the symptoms are of such nature as to suggest to the patient that they arise *because of* disturbed cardiac function. As a result a vicious circle is set up, consisting of anxiety producing symptoms which, in turn, produce anxiety. There is seemingly no effective homeostatic mechanism at work. The very patient who is most fearful of heart disease is the one most likely to develop symptoms which further fix the thought of heart disease in his mind and perpetuate his fears.

## Manifestations

The manifestations of iatrogenic heart disease are those commonly produced by anxiety. Palpitation, fatigability, breathlessness and precordial pain are the most prominent symptoms and are perfectly suited to verify the thought of heart disease in the mind of the patient. As in any of the other forms of anxiety neurosis, however, there may be many other manifestations, including apprehension, trembling, dizziness, syncope, paresthesias, tachycardia, and cold, clammy hands and feet.

Disturbances in breathing may take several forms. The most common is the sensation that the air taken into the lungs is insufficient, leading to deep "sighing" respirations. The patient usually calls this "shortness of breath," but careful inquiry will reveal its true character. When carried to excess it may lead to hyperventilation alkalosis, which can produce further distressing symptoms. At times the anxious patient will speak, not of "shortness of breath," but of "smothering spells," which represent the same phenomenon of "sighing" respirations but which occur in an acute and rather terrifying form. Actual exertional breathlessness is commonly present. To a large extent this is due to the lowered state of physical "condition" from restriction of activity, similar to the deterioration in the "wind" of any athlete who fails to "keep in condition." The respiratory inefficiency which has been shown to result from anxiety [13, 14] may also contribute to the dyspnea.

Undue fatigue is commonly interpreted by the patient as due to some cardiovascular abnormality, particularly "low blood pressure." Actually, however, it is one of the most frequent manifestations of emotional illness and is a major complaint in over 90 per cent of the patients diagnosed as neurocirculatory asthenia.[11, 15, 16] The fatigue may be noted principally on effort or under nervous tension, or may be more protracted. In the latter case there is characteristically a diurnal swing, with fatigability present on awakening but decreasing later in the morning as the patient swings into his day's activities, and then tending to increase again in the late afternoon or evening. To a large extent this symptom is purely subjective and psychologic. As an example, the early morning fatigue is often the conversion of the lack of enthusiasm with which the patient faces the forthcoming day. In this regard Shands and associates [17] have reported that "the feeling of tiredness is specific for certain activities; whereas at times the patient can carry on strenuous activities of one sort, other forms wear him out at once." This is substantiated by the oft-seen instance of the neurotically tired individual who is dramatically revived by an invitation to a card game, dance or other pleasurable activity, which he can then pursue into the late hours without any thought of fatigue. There may also, however, be physiologic changes concerned in the production of this symptom, such as hypoglycemia [18] or disturbed lactate metabolism,[19] though the exact rôle that these factors play is not yet clear.

Precordial discomfort is a symptom which is very potent in causing the thought of heart disease to become fixed in the mind of the patient. In World War II Friedman [12] and Wood [11] independently analyzed the precordial pain occurring in soldiers with neurocirculatory asthenia in the American and British Armies, respectively, and arrived at similar conclusions. Three types of pain have been delineated. One is the sharp momentary jab of pain associated with the occurrence of premature beats. A second type of precordial discomfort is also composed of sharp, piercing, transient pains, but with regular cardiac rhythm. This pain probably arises in the intercostal muscles, being produced, through an incompletely explained mechanism, by the impact of the heart against the chest wall. The third type is a dull prolonged precordial ache which occurs largely in those individuals who use only the upper half of their chests in breathing. Friedman [12] concluded that this pain was due to excessive use of the intercostal muscles in respiration. Wolf [14] experimentally produced this costal type of breathing in patients by producing emotional tension, and he observed fluoroscopically the development of sustained diaphragmatic contractions, to which he attributed the pain.

## Course and Prognosis

Untreated iatrogenic heart disease tends to perpetuate itself because its very symptoms continue to suggest cardiac abnormality to the patient and thus maintain his fears. There is no mortality problem, but the morbidity may be greater than in the average case of organic heart disease. This may lead to economic, social, family and military implications, many of which are so interwoven that they cannot be separately tabulated.

The prognosis in treated cases depends on many factors. One is the duration of the process, since it is usually easier to eradicate in its early stages than when the patient has been conditioned for years to cardiac invalidism. A second factor is the emotional make-up of the patient. Many of these individuals are basically psychoneurotic, and some cannot be persuaded to relinquish this outlet. There are others not intelligent enough to understand, for example, how they can have pain "around the heart" without having a bad heart, regardless of how simply and clearly the true situation is explained to them. One will meet all types of people in the category of iatrogenic heart disease. Fortunately many are intelligent, relatively stable people who have been frightened into the vicious circle of anxiety, symptoms and anxiety, and are happy to be rescued.

## Diagnosis

Diagnosis is based upon three criteria: (1) The patient must have symptoms; (2) the symptoms must be due to fear over heart disease, brought about by the words or acts of the physician, but (3) the heart itself is normal,

though there may be questionable or equivocal symptoms or findings. Indeed, those individuals with equivocal findings that lead to the erroneous impression of heart disease will perhaps constitute the bulk of cases. Among these are the people with innocent murmurs, minor electrocardiographic variations, unimportant blood pressure fluctuations and benign arrhythmias. Then, too, there is a large group of individuals with normal cardiovascular findings but with cardiac-like symptoms of noncardiac origin. This group includes, among others, those with thoracic pain of gastrointestinal or nerve root origin, and, importantly, those whose original symptoms are due to an anxiety neurosis.

## Treatment

One of the major reasons for singling out iatrogenic heart disease is that it can be treated, and in a relatively specific manner. I believe that iatrogenic heart disease holds the same relationship to other cardiac neuroses as the "benign nervous states" of Allan and Kaufman [20] to their "psychoneurosis." They state: "For these cases of 'benign nervousness' there is no diagnostic term which has been generally accepted, but they must be distinguished from the other groups in the consideration of diagnosis, treatment, and prognosis. . . . Several points of difference have been outlined elsewhere. A neurosis is largely dependent on *an intrinsic defect in the personality* * of the person and is usually considered to be an expression of subconscious emotional conflicts. . . . Benign nervousness, on the other hand, is largely the result of *external factors*. . . .* The reaction to reassurance in these two types of cases is decidedly different. The neurotic patient is disappointed when the physician tells him that the physical examination gave negative results. . . . The patient with benign nervousness expresses satisfaction if informed that there is nothing physically wrong. He can recover without any special psychotherapy other than sufficient time with the physician. . . ." I do not know if psychiatrists generally accept this concept, but it has a proved validity in everyday clinical practice. There is an analogous distinction between the general cardiac neuroses and those of iatrogenic origin. In the former there are likely to be deep personality disturbances which require extensive psychotherapeutic measures. In the latter, where the precipitating factor is obviously on the surface, the method of approach in treatment is similarly superficial.

Successful treatment depends on successful reassurance of the patient. To this end it is necessary that the physician undertaking this treatment conduct an examination sufficiently exhaustive to convince himself and, perhaps even more, the patient, that the heart is sound. This is one time when the use of all the supplementary tools of cardiovascular study can be encouraged, because of the extra authenticity it lends to the examiner's

* Italics theirs.

pronouncements. The treating physician has one strike in his favor if the patient originally considers him to be a higher authority than the doctor who provoked the fear of heart disease. In the absence of such prestige, however, an efficient thorough examination will go a long way toward impressing the patient that the final diagnosis is based upon a firm foundation.

The reassurance, to be effective, must be clear-cut. There can be no hedging. Alvarez [3] states: "A physician is never going to cure neurosis unless he is positive when he says that the examinations showed nothing wrong. If he hedges and straddles and tries to keep a line of retreat open in case things go wrong, the worried patient will never be cured."

As far as possible we should reconcile the differing medical opinions the patient has received, not only because it is tactful but also because it may make patient acceptance more likely. There are times, however, when we cannot possibly make such reconciliation but must bluntly and firmly disagree with the pronouncements of a previous medical attendant. Under such circumstances we can follow no other course, because our first concern must be the patient's health.

Along with emphatic reassurance as to the soundness of his heart, the patient should be made to understand how his symptoms have resulted from his fears. The simple admonition, "It's all in your head" or "It's just your nerves," is entirely inadequate. As a matter of fact, it is often worse than useless, actually serving to make the patient refractory to further suggestion, since he is apt to feel that such a statement implies low intelligence, weak will power, nonexistent symptoms or even willful malingering. I have a notion that the patient is entitled to such an attitude, for the practitioner who brushes him off in that manner is actually likely to feel just that way about the neuroses. The physician must first of all accept, and convince the patient that he accepts, the symptoms as being real. Then he must point out to the patient that the symptoms are caused, not by any disease of the heart, but by fear. The physician should explain briefly or fully, according to the intellectual capacity of the individual patient, the mechanisms whereby fear can produce the symptoms he experiences.

The patient must be made to know that his symptoms are not dangerous to life, regardless of how distressing they may be subjectively. He should know that the symptoms will leave if his fears are relieved but may persist if he retains any fear at either a conscious or a subconscious level. It is important that he be instructed to carry on in spite of symptoms, should they occur. Any attempt at compromise, as by instruction to "take things easy," or by giving "a little heart tonic," may be disastrous by negating the assurances of cardiac soundness.

There are times when we must unqualifiedly assure the patient that his heart is absolutely normal when actually there may be slight doubts in our minds and, incidentally, on our private records. If kept there, the doubts will not harm the patient, but if they are transmitted to him they may well defeat all our therapeutic efforts.

## Prevention

Prevention is the most important aspect of the entire problem, since iatrogenic heart disease is potentially 100 per cent preventable. Probably the most fruitful approach is to analyze the various reasons why the physician erroneously makes the patient feel that heart disease is present, since recognition of each reason will automatically suggest its remedy. I would list five reasons as possible initiating factors:

1. Misinterpretation by the patient of innocuous statements.
2. Ill-considered remarks of the physician.
3. Ill-considered acts of the physician.
4. Error by the physician in interpreting symptoms.
5. Error by the physician in interpreting findings.

1. The problem of the patient's misinterpretation is common to every phase of medicine. An earnest practitioner may say to a patient that his heart rate is slow, his heart is small, or his blood pressure is low, in each case knowing that the finding is a favorable one. Not understanding this, however, the patient may interpret it in an unfavorable light and thereafter feel certain that the doctor told him he had heart trouble. The remedy is not simple, because the potentialities are unlimited. The physician who is constantly aware of this danger, however, will take pains to speak in such a way that his remarks cannot be misinterpreted. In the example given above, the careful doctor would explain that the slow rate, small heart or low blood pressure is the ideal finding that he sought and that convinced him the heart is normal. He may, furthermore, ask the patient to repeat in his own words the doctor's advices, to make sure he understands them as intended. Extra caution at the time of the original interview is much more valuable than later attempts to correct an erroneous impression.

2. A second method by which iatrogenic heart disease can be initiated is through the ill-considered remarks of a physician. It would be merely scratching the surface to list such examples as, "I never saw a worse heart than yours," "You have six months to live," or "You might have a stroke any minute." Such remarks are of questionable propriety in the presence of organic heart disease. They are reprehensible when no disease is present and a well man becomes a sick man thereby.

In speaking of two patients who became disabled in this way, Thomas[9] said: "In these two cases the symptoms became apparent to the patient directly following ill-considered remarks of the physician which resulted in anxious concern and depression. The power that even their lightly spoken words have to instil fear into the minds of patients often is overlooked by physicians. . . . Therefore, it becomes necessary for the physician to be aware of all the little or big ideas that may act as entering wedges for fear into the patient's consciousness and avoid them or neutralize them on the spot."

The remedy, again, is caution in speaking to patients. If one should be

careful that the patient does not misinterpret an innocuous remark, one should be immeasurably more careful to avoid making tactless statements which, even at face value, will produce unwarranted distress.

3. A third method is through the ill-considered acts of the physician. In some cases the doctor realizes the act he is performing, though not recognizing its potential harm. One such act is the prescription of limitations, which may be of any degree from "taking things easy" to complete bed-rest. Others include the prescription of digitalis or the prescription of frequent return visits for heart examination. There are other acts, however, that the physician may perform unknowingly but that may as surely instil the feeling of heart disease into the mind of the patient. Thus, if the doctor calls in a colleague to "have a listen," the seed has been sown. If this is followed by a technical discussion in his hearing, it is the rare patient who will understand, without outside assurance, that he has a normal heart. The ordinary layman is likely to feel that a cardiac examination consists of one blood pressure determination and a short application of the stethoscope to the left breast. If he sees the doctor measure the pressure in both arms and explore several auscultatory sites on the chest, altering position and respiratory phases, he is likely to receive an ominous impression. Actually, the physician may simply be a meticulous examiner, but the patient's natural thought is, "He has found something wrong." The same result may ensue from the use of extra instrumental aids, like the roentgen-ray and the electrocardiograph.

The remedy in either case is clear. The unwitting production of fear can be avoided by recognizing the psychology of the patient and anticipating what is likely to prove disturbing to him. After that, one first deletes whatever is possible, though never compromising with thoroughness. An example of what can be deleted is the technical discussion within the patient's hearing. Then one explains those acts which may appear as unusual to the patient, along with proper reassurances. Thus the patient is very happy to hear, after long auscultation, that it was occasioned not by the doctor's finding something wrong but by his desire to be entirely certain that no abnormality could be found even on the most rigorous searching.

The remedy for the conscious but ill-considered acts which directly suggest heart disease lies in educating physicians to a more liberal and optimistic attitude toward heart disease. For a long time rest and digitalis constituted the bulwark of cardiac therapy. Unfortunately, that thought is still too prevalent today, though it is heartening to see a different attitude emerging. Insofar as digitalis is concerned, it is now quite clear that the indication for its use is heart failure, not a murmur or coronary artery disease or hypertension. There is thus no justification for its administration to people who have normal hearts with some equivocal findings. The laying of the bugaboo of rest started much later than the clarification of the rôle of digitalis, and it is just now gaining momentum. For a long time it was heresy to question the importance of rest in the management of heart disease. Fortu-

nately, though, in recent years this aspect has been reëvaluated, and a progressive retreat from the stringent limitations of the past is under way. The orthopneic cardiac in failure is now allowed to sit up comfortably in a chair rather than suffer in bed.[21] Use by the patient with an acute myocardial infarction of a bedside commode for defecation is now considered preferable to his straining on the bedpan and rupturing his heart.[22, 23] In such instances concrete proof is easily available, and progress should be rapid. But when it comes to long-term management of heart disease, it is more difficult to assess the value of rest. Is a man who has once had a myocardial infarct better off if he refrains from working thereafter? Or is his life expectancy lengthened by working 20 hours a week instead of 40 hours? Should a young man with mitral stenosis Class I functional capacity be denied the privilege of bowling one night a week when he can do so without incurring any discomfort? In the past the tendency was to place artificial restrictions on the cardiac patient in the hope of protecting his heart. But carefully analyzed experience has not borne out the value of such restrictions. On the contrary, not only did it fail to prolong life, but it so damaged the patient's morale that the surviving years were not happy ones.

And so the pendulum began to swing. Today the weight of authority is moving in the opposite direction. Now the cardiac patient is encouraged to perform physical activity just short of his level of tolerance, as determined by his own symptoms.[5, 8, 24] Unfortunately, this attitude is still largely a top-level one.[5, 8, 21, 24, 25, 26] When it permeates the entire profession, the physician will no longer hogtie his cardiac patients with unreasonable restrictions. And when he can be that liberal with proved heart disease, he will not feel constrained to prescribe limitations in his doubtful cases just to "play safe." The young woman with a systolic murmur but without any other indication of heart disease will not be told she should never become pregnant, as has occurred in the past. This fortunate result will occur even without any special progress in diagnostic acumen when the practitioner realizes that, since organic valvular heart disease is no bar to pregnancy, he should also not restrict doubtful disease. I am certain that when all physicians are educated to a more liberal and optimistic attitude toward heart disease, there will be much less psychologic crippling through ill-considered acts.

4. The fourth method whereby iatrogenic heart disease may be initiated is through the misinterpretation of symptoms. The process of fixation is ordinarily easy in these cases. The patient who comes to the doctor with precordial pain, for example, is usually already fearful that it means heart disease. Actually, it may be due to any one of a number of other conditions, but if the doctor mistakenly interprets it as evidence of heart disease, the patient has no reason to doubt the diagnosis, and his own fears become fixed. The symptoms commonly misinterpreted are precordial pain, breathlessness, palpitation, fatigue, dizziness and fainting.

The remedy is self-evident. Each complaint of the patient must be carefully analyzed. There are no symptoms that belong exclusively to heart disease. The patient may come and complain of pain "around the heart." But the physician must know that such pain need not arise *in* the heart. Of utmost importance in deducing the significance of a symptom is knowing the characteristics of that symptom. And since he does not himself experience it, the physician must obtain the description from the patient. The doctor cannot justifiably make a proper diagnosis if he blandly accepts the patient's statement that he has "pain around the heart." He cannot begin to know what that complaint means until he learns at least where the pain is located, where it radiates, when it occurs, what initiates it, how long it lasts, what relieves it and what other symptoms are associated with it. Similarly, he cannot properly evaluate the complaint of "shortness of breath" without probing behind those words. He will often discover that with this phrase the patient is describing the typical "sighing" respirations of psychogenic origin, and he will sometimes discover that a middle-aged man has lost the "wind" of his youth, though he does not suffer in comparison with his contemporaries. In addition to a careful analysis of the symptoms, the entire process of history-taking and examination must be thorough in order to detect the significant clues to the proper diagnosis. There is no short-cut. Instrumental aids may help, but they do not replace the clinician's brain. The most careful and intelligent diagnostic studies will probably never achieve perfection, but it is not too much to set our goal as near perfection as we can come.

5. The fifth method is the misinterpretation of findings. Here belong the innocent murmurs which become "leaky hearts," and the benign pulse irregularities of premature beats which become "heart blocks," and the $Q_3$ electrocardiograms which become "coronary disease," and many others.

The remedy here is two-fold. First, the practitioner must have a basic knowledge of diagnostic fundamentals. He must know that there are innocent as well as pathologic murmurs. He must know that the commonest cause of intermittence of the pulse is the premature beat, and know what steps to take to differentiate it from heart block. He must know, if he interprets electrocardiograms, that a $Q_3$ is often present with normal hearts. *He should have relatively as much "cardiac" knowledge if he is going to diagnose heart disease as he would wish to have "surgical" knowledge if he were going to open the abdomen.*

Second, as mentioned previously in relation to prescribing digitalis and limitation of activity, the physician should be educated to a more liberal attitude in the diagnosis of heart disease. A fair rule-of-thumb might be to give the patient the benefit of the doubt in every doubtful case. Thus, if the patient stands to benefit by positive action when the diagnosis is in doubt, then disease should be diagnosed. An example of this might be a patient with suspected subacute bacterial endocarditis with persistently negative blood cultures; he should be given antibiotics on a presumptive diagnosis.

Much more commonly, however, the patient would be psychologically benefited and at the same time would not be deprived of any effective therapy if the physician decides to diagnose "no heart disease." If we use the borderline systolic murmur in the adult as an example, what are the alternatives? If the murmur later emerges as due to organic valvular disease, it is extremely doubtful that any therapy would have improved the prognosis, or lack of therapy worsened it. On the other hand, if future observation proves it to be benign, all therapy was needless and, worse, the psychologic impact was harmful in greater or less degree.

Although such liberality is not sufficiently widespread as yet, it is surely coming. It is a favorable omen to find three such references published within four months in the *Annals of Internal Medicine* in 1951, by such cardiologists as Parkinson,[24] Rosenbaum [27] and White.[26] It is also encouraging to see that the special article on Clinical Progress in the March 1952 issue of *Circulation,* the journal of the American Heart Association, is entitled "Needless Restrictions Imposed on Cardiac Patients." [28] The adoption of these liberal-minded teachings in everyday practice will certainly lead to happier results.

The following case almost epitomizes the subject of iatrogenic heart disease.

### Case Report

A 31 year old white man came to the office in June, 1951, in an extremely agitated and apprehensive state. He had collapsed at work three days earlier because of dizziness, and he had been unable to return to work because of severe dizziness, weakness and breathlessness. In his mind, of course, he knew that his heart had given out and his days were numbered.

The story of how this young man came to be in such a state is of sufficient interest to warrant its detailed description. The first incident occurred in 1940, when his home doctor found a heart murmur in the course of a routine examination. Apparently it made little impact on either one. The doctor told the patient that it would not keep him out of military service, and it didn't. Two pertinent incidents occurred during his Army career. First, he failed to bounce back to normal vigor with sufficient rapidity upon recovery from pneumonia; he was subjected to a thorough clinical, electrocardiographic and roentgenologic study and was told that he had a "soldier's heart." Second, he collapsed several months later following an unusually strenuous physical exertion and was taken to a dispensary, where the doctor gave him some digitalis. He adjusted well thereafter and served out the rest of the war without further difficulty, though he admits to occasional worry over his heart during that period.

After discharge he came home and went to work. He was an ambitious man and drove himself hard trying to build up a remunerative bread route. As a result he lost some weight, felt tired and became irritable. So he visited his original doctor, who listened to his heart, shook his head grimly, and said, "A lot has happened to this heart since the last time I examined you. You must give up smoking and you must stop working immediately." At that moment the patient developed iatrogenic heart disease and thereafter lived with the spectre of sudden death.

He gave up his job and moved to Arizona, where he worked at odd jobs, all light work. Only once did he try heavy work. On that occasion he was hired to

load, drive and unload a heavy truck. On the third day of this he found himself in California with symptoms of dizziness, weakness and palpitation, so he consulted the nearest physician. This doctor bluntly told him that his heart was in terrible shape, that he must go right to bed and must stop tobacco, coffee and alcohol. He stuck to very light jobs thereafter. During the time he was in Arizona he consulted three different physicians about his heart. One said he couldn't hear a thing. The second said he had an "athlete's heart," and showed him a textbook statement that this is not fatal. The third was a specialist, who told him he had some minor thing that thousands had and that it meant nothing.

Since he felt no better in Arizona, the patient finally returned home in 1950. His first act was to return to his original doctor, who listened to his heart and said it was much better. Thus encouraged, he found work as a glazier but, as instructed by the doctor, returned every three months for a "check-up," which consisted of a brief auscultation over the precordium. On the strength of this kind of examination the physician gave him a progress report each time. On the last two occasions the reports had been unfavorable, and the man had been completely disabled for three days when I first saw him.

Anatomically and physiologically he had a perfectly normal heart. There was an inconstant faint blowing systolic murmur at the pulmonic area, such as is universally recognized as being nonpathologic in origin. All other findings were completely normal. There was one unusual finding which may have accounted for the erroneous diagnosis of heart disease and also for the apparent variations in the findings from one examination to the next. When the patient first lay down on the examining table he abducted his left arm and cupped the left hand under the back of his head. This produced a loud harsh systolic bruit, maximal just above the center of the clavicle, and audible in progressively decreasing intensity as far medially as the pulmonic auscultation area. The bruit disappeared completely on lowering his arm, and the phenomenon could be consistently repeated at will. Apparently the abduction of his arm was constricting the subclavian artery sufficiently to produce a bruit, in a manner analogous to the production of the Korotkov sounds in sphygmomanometry.

Despite the fact that his iatrogenic heart disease had already been present for five years, the outcome here was excellent. To a large extent this was probably due to the fact that the patient was able to evaluate the questionable finding himself and see that it could not possibly be a sign of heart disease. To accomplish this I gave him the stethoscope and had him listen in the supraclavicular region as he alternately raised and lowered his arm, causing the bruit to appear or disappear, respectively. Then I had him listen to his Korotkov sounds, and pointed out how the bruit was obviously of similar origin. With this foundation it was relatively easy to convince him that his heart was normal, that the previous diagnoses of heart disease were undoubtedly based on erroneous interpretations of the bruit, and that his symptoms were entirely due to fear. The patient was pathetically happy over the result. He has been working steadily since that time without symptoms and without concern over his heart.

## Summary

Iatrogenic heart disease is an illness in which symptoms referable to the heart, or symptoms interpreted by the patient as such, are produced as a result of the words or actions of a physician. The condition is an anxiety neurosis caused by fear of heart disease. The symptoms, particularly precordial discomfort, breathlessness, palpitation and fatigue, are unfortunately

perfectly suited to verify the thought of heart disease in the mind of the patient and thus to perpetuate the disorder.

Successful treatment depends on recognizing the illness and reassuring the patient adequately. He must be assured that his heart is normal, that his symptoms are due to fear, and that the symptoms are not dangerous to life.

Prevention is the most important aspect. To prevent the production of iatrogenic heart disease, the physician is urged to be cautious in the following five spheres, which may act as initiating factors:

1. Misinterpretation by the patient of innocuous statements.
2. Ill-considered remarks by the physician.
3. Ill-considered acts by the physician.
4. Error by the physician in interpreting symptoms.
5. Error by the physician in interpreting findings.

Iatrogenic heart disease is the source of considerable morbidity, and a constant awareness of its potentiality should do a great deal toward preventing its occurrence.

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# THE TREATMENT OF ANGINA PECTORIS WITH KHELLIN*

## PART II

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IN Part I of this paper [1] we reported the results of treating a series of 42 patients afflicted with the anginal syndrome with khellin (visammin) in the form of Ammivin®. The present communication is concerned with a similar series of 42 patients with angina pectoris who were treated with a brand of khellin known as Khelloyd®.† We discussed previously the history, pharmacology and clinical aspects of the drug, and this material will not be repeated.

### METHOD

Forty-two patients with the anginal syndrome due to arteriosclerotic heart disease were selected to receive khellin orally and/or parenterally. These patients constituted a different group from the ones treated in Part I of this study, but the two groups were similar in age, duration and severity of the disease, and complications. The diagnoses were substantiated by careful history and complete cardiac evaluation, and many of the patients had been under observation and treatment with other drugs for several years. The group was comprised of 32 males, 14 of whom had old myocardial infarctions, and 10 females, three of whom had old myocardial infarctions. The patients ranged in age from 36 to 82 years, and the duration of the angina was from one month to 15 years, with an average of three years. Each patient was instructed to record the number and severity of anginal attacks and the number of nitroglycerin tablets taken daily. All patients except a few who were dangerously ill were observed during a control period in which they received placebos identical in appearance to the tablets containing the drug. They were then started on khellin and observed for varying periods up to one year.

Therapy was instituted by having the patient take 25 mg. of khellin a day for the first week, and the dose was thereafter increased at weekly intervals by 25 mg. a day until a therapeutic response or a reaction occurred. In the event that the patient suffered undesirable side effects, the dose was decreased in an attempt to arrive at a nontoxic but therapeutically effective dose for that individual. When the therapeutic dose exceeded the toxic

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† 50 mg. uncoated tablets of khellin supplied by Lloyd Brothers, Cincinnati, Ohio.

dose for a given patient, the khellin was discontinued if the reactions were severe, but some patients with less pronounced side effects continued to take the drug in spite of them.

A parenteral solution containing 40 mg. of khellin per cubic centimeter was employed as adjunctive therapy in six patients. These patients received 18 intramuscular and seven intravenous injections of 2 c.c. each, given at semiweekly or weekly intervals.

The khellin was administered continuously in most cases, intermittently in others, and some patients received other coronary vasodilators, such as erythrityl tetranitrate, either alternately or concurrently with the khellin. The clinical response to khellin was classified as favorable if the frequency or severity of the anginal pains were diminished, even if side effects were noted, as unfavorable if the reverse occurred, or as unchanged. All patients were reëxamined at intervals of one week or less, and all had periodic electrocardiograms, orthodiagrams and ballistocardiograms.

## Results

*Reactions:* Of the 42 cases, 21 patients (or 50 per cent) developed one or more undesirable reactions on a minimal therapeutic or a subtherapeutic dose of khellin. It was of course possible to produce reactions in all of the patients if a large enough dose was given. All of these 21 patients had nausea, mild in nine and severe in 12, being accompanied by vomiting in eight. No other reactions were noted.

Various methods previously described [1] were used in an attempt to diminish the number and severity of the side effects, but we could determine no particular benefit from any of these measures.

The parenteral medication was tolerated fairly well, although one patient became nauseated after each injection. No local reactions were noted at the site of the intravenous injections, but one patient developed sloughs 1 cm. in diameter at the sites of two intramuscular injections.

*Clinical Response:* Twenty-five of the 42 patients (or 60 per cent) experienced a decrease in the number and/or severity of the anginal pains and therefore obtained a favorable response. This figure includes some who had reactions, several of whom were forced to discontinue the drug. Two patients (or 5 per cent) showed an unfavorable response, with increased pain, and 14 patients (or 33 per cent) were unchanged. The remaining 2 per cent represented one patient who died from an acute myocardial infarction during the course of treatment after showing marked initial improvement.

Of the 17 patients who had old myocardial infarctions, a favorable response was obtained in seven patients (or 41 per cent). The response to the drug was not affected by the sex of the patient or by the age, except that the group with old myocardial infarctions showed a less favorable response and these were in an older age bracket. Some patients reported an improve-

ment in their pain following a periodic intramuscular injection, although they were already taking the maximal amount that could be tolerated orally, which corroborates the fact that some patients could not tolerate an effective therapeutic dose by mouth.

In four patients the response to khellin could be described as dramatic as the khellin quickly abolished their pain when other medication had failed. Nine patients who were unable to tolerate khellin in a dosage high enough to prevent their attacks of pain were maintained on a subtherapeutic dose of khellin and were given erythrityl tetranitrate concomitantly. They had less pain while on this combination than while on either drug alone.

There was noted a wide individual variation in the amount of khellin necessary to produce a clinical response and also in the amount that would produce side reactions. The highest dose we were able to maintain for any length of time was 100 mg. per day. Some patients were able to tolerate only 20 mg. a day; indeed, even this small amount nauseated others. The average maintenance dose in those patients who had minor or no reactions and who were able to continue the drug over a period of months was 75 mg. daily. It was thought that this was far below the effective therapeutic dose in many cases.

The drug was given to three persons with an acute myocardial infarction not included in this series, but in two of these it induced severe vomiting, the control of which necessitated the use of narcotics, and it was felt that the deleterious effect of these reactions outweighed any beneficial vasodilating effect that was obtained.

## Discussion

Slight differences in the percentage of favorable results and in the percentage of untoward reactions are noted when these results are compared with those reported in Part I of this paper, but these differences are not considered to be statistically significant.

Since the first group of patients received coated tablets and the second group received plain tablets of khellin, the use of the coated tablet evidently affords no particular advantage or disadvantage in regard to the clinical response or side effects. In fact, there would appear to be little or no choice between the two brands of khellin employed in these studies.

The discrepancy between the reports from this country and those from Egypt concerning the incidence of reactions to khellin remains somewhat of a mystery. In addition to the possibilities we considered before,[1] another one is suggested in an article by Schoenberg and Sina.[2] They point out that a species of a plant very similar in appearance to *Ammi visnaga* grows in the Mediterranean area. This plant, called *Ammi majus,* contains xanthotoxin, which has a strong emetic action and has a structural formula very similar to that of khellin. Some of the products of khellin on the domestic market have been assayed and found to contain a considerable percentage of

this emetic substance. This could not be the entire answer, however, as the product used in the present study contained no xanthotoxin when assayed, but still produced nausea. This same brand of khellin was employed by Scott and Seiwert,[3] who also noted frequent reactions, although their patients were able to tolerate somewhat higher doses without reactions than were our series of patients.

In our work the reactions to khellin appeared to be divided into two general categories. One type of reaction seemed to represent a hypersensitivity to the drug and was manifested by several patients who could not take even a small amount of khellin without becoming nauseated. The other type of reaction was more in the nature of an overdose for a given individual and was exemplified by those patients who could take moderate amounts of the drug but could not tolerate what was considered to be a therapeutic dose.

Our observation that parenteral khellin therapy in the absence of oral therapy may produce nausea was recently confirmed by Kleiber,[4] who encountered several instances of nausea while treating 18 patients with an intramuscular suspension of khellin. The nausea produced by parenteral therapy could be engendered either by a direct action on the central nervous system or by the transportation in the blood stream of khellin to the gastrointestinal tract.

One other factor in regard to the reported differences in the incidence of reactions might be mentioned. Some studies, including our own, were conducted on private patients, while others were carried out with clinic patients. Ideally, there should be no difference in the responses of the two groups, but it is quite possible that clinical patients might hesitate to complain of side effects and might be more likely to associate them with the disease than with the therapy.

A comparison of our clinical results with those of other workers in this country and in Egypt is discussed in Part I and does not require repetition here. Nothing in the results of the present study would seem to require us to alter our conclusions previously expressed, including our preference for erythrityl tetranitrate for the routine treatment of the anginal syndrome. Taking into account the difficulty in the clinical evaluation of any coronary vasodilator, we still feel that khellin is of value as a dilating agent, especially in selected patients who fail to respond to other types of therapy; and that if the reactions could be reduced in number and severity, the drug would assume a more important rôle in the treatment of the anginal syndrome.

## Summary

1. Forty-two patients with the anginal syndrome were treated with khellin (visammin) orally or parenterally or both for periods averaging six months, and the clinical response was gauged by the number and severity of anginal attacks and the number of nitroglycerin tablets taken.

2. In 50 per cent reactions in the form of nausea and vomiting were

encountered, the reactions in 12 patients being severe enough to require cessation of therapy.

3. Twenty-five patients (or 60 per cent of the group) had a favorable response to the khellin, two patients (or 5 per cent) had an unfavorable response, and 14 patients (or 33 per cent) were unchanged. One patient (representing the remaining 2 per cent) died before the study was completed after showing marked initial improvement.

4. The above results are not essentially different from those obtained with another brand of khellin, as previously reported in Part I of this paper, and are in general agreement with those reported by the majority of other investigators in this country.

5. Khellin is of value in the treatment of the anginal syndrome but will not replace the other vasodilators to any great extent unless a method of decreasing the incidence of side effects is discovered.

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# SPONTANEOUS ADRENAL HEMORRHAGE IN THE ADULT: LITERATURE REVIEW AND REPORT OF TWO CASES*

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IN this report a study is made of spontaneous adrenal hemorrhage only in the adult. Direct causes of hemorrhage, such as local infection, septicemia, neoplasm and trauma, have been eliminated. Using this criterion, a review of the literature uncovered 22 cases previously reported, to which the two new cases herein described are added. The 24 cases are listed in table 1.

## CASE REPORTS

*Case 1.* A 58 year old white female was admitted to the hospital in March, 1950. She had been asymptomatic except for a history of hypertension for several years and a mild, nonproductive cough for a few days. Ten hours before admission she developed aching in the muscles of the calves of the legs and a headache. One-half hour before admission she suddenly became disoriented, unable to speak, irritable and somewhat excited. Upon arriving at the hospital the patient's condition was almost terminal. The skin showed a mottled cyanotic color. She was not unconscious but was completely disoriented and unresponsive. When disturbed by examination she became very restless. Temperature was 104.8° F.; pulse, 94; respirations, 28; blood pressure, 160–190/80 mm. of Hg. The remainder of the examination was not revealing except for marked generalized obesity and a few inconstant coarse râles at the right lung base. The patient never responded and died four hours after admission.

At postmortem examination the body was 64 inches in length and about 250 pounds in weight. The skin of the head, trunk and extremities showed a deep mottled cyanosis. No petechiae or purpuric areas were noted. There were no other external gross abnormalities.

The two adrenal glands appeared twice normal size. Both the glands and the fat tissue immediately surrounding them were incorporated in hemorrhage. When the glands were dissected free they were found to be completely destroyed, necrotic, friable and of deep red hemorrhagic appearance. The normal architecture was not grossly distinguishable. The glands crumbled under slight pressure. Microscopically, hemorrhage was seen throughout the cortex, under and into the capsule. Nearly all of the cortex was necrotic. Only small isolated islands of cortical cells were present here and there between fresh hemorrhage. The center (medulla) of the gland was completely destroyed and replaced by a network of amorphous eosinophilic staining matter in which there were ghost cells, destroyed red blood cells with hemosiderin deposits, and polymorphonuclear and lymphocyte infiltration of a moderate degree.

The remaining positive pathologic findings included: (1) a few loose pleural adhesions over the lateral aspects of both lungs, with congestive changes at the lung bases; (2) enlarged hypertrophied left ventricle, with bulging of the interventricular

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TABLE I

Case Reports from the Literature of Spontaneous Adrenal Hemorrhage

| Author | Age | Sex | Adrenal Involved | Pathology in Adrenals | Abdominal Signs and Symptoms | Remarks |
|---|---|---|---|---|---|---|
| Goolden[1] (1857) | 46 | M | Both | — | Epigastric pain | None |
| Arnaud[2] (1900) | 17 | F | Right | — | Epigastric pain and tenderness | Occurred 11 days after a burn |
| Lavenson[3] (1908) | 44 | F | Both | Extensive hemorrhage. Thrombosis of both adrenal veins | Epigastric pain, tenderness and rigidity | Also had pancreatitis |
| Michaux and Marsset[4] (1923) | 74 | M | Both | — | Tenderness both upper quadrants | Also had chr. nephritis |
| Farr and Semsroth[5] (1927) | 34 | M | Both | Hemorrhage in adrenals, retroperitoneal and peritoneal spaces | Epigastric and RUQ pain. Tender, rigid and distended. Mass right iliac fossa | None |
| Pearl and Brunn[6] (1928) | 45 | M | Both | Hemorrhage in adrenals and surrounding fat. Thrombosis of many adrenal veins | Pain both upper quadrants, flanks and back. RUQ tenderness | Chr. thrombophlebitis rt. leg. Syphilis treated 2 years previously |
| Taylor[7] (1930) | 54 | F | Both | Necrosis and hemorrhage replacing adrenals. Hemorrhage surrounding fat | Abdominal pain and vomiting | Intestinal diverticulosis, P.A. and A.S.H.D. |
| Seligman[8] (1932) | 42 | F | — | Pronounced hemorrhage | Abdominal distention | Patient in coma. Has hypertension and gen. arteriosclerosis |
| Hall and Hemken[9] (1936) | 18 | F | Both | Hemorrhage in medulla and cortex, mostly on left. Thrombosis of some medullary veins | Left lumbar pain | Hyperemesis gravidarum in first trimester |
| Barsoum[10] (1936) | 30 | M | Both | Diffuse hemorrhage, most marked in the medulla | Generalized abdominal pain and tenderness | None |
| Altschule[11] (1939) | 72 | M | Both | Hemorrhage in medulla, cortex and capsule. Thrombosis of adrenal veins | Epigastric pain and tenderness Abdominal rigidity | Had carcinoma of lung |
| MacKenzie and Park[12] (1941) | 35 | F | Both | Hemorrhage throughout adrenals and in pericapsular area. Blood tinged fluid in abdomen | — | Death following 36 week old still birth. Bilateral pyelonephritis |
| Leone[13] (1941) | 43 | M | Both | Hemorrhage in medulla and cortex | — | Treated for syphilis 10 yrs. prior. Became seronegative |

TABLE I—*Continued*

| Author | Age | Sex | Adrenal Involved | Pathology in Adrenals | Abdominal Signs and Symptoms | Remarks |
|---|---|---|---|---|---|---|
| Keele and Keele[14] (1942) | 32 | F | Right | Infarction due to thrombosis rt. adrenal vein. Thrombus protruded into vena cava | RUQ pain and tenderness | 8 months pregnant |
| Thorstad[15] (1942) | 40 | M | Right | 5 cm. hemorrhage with necrosis of cortex | Epigastric pain | Pneumonia and paroxysmal auricular fibrillation |
| Williams and Ellis[16] (1944) | 23 | F | Both | Hemorrhage throughout. Pericapsular hemorrhage on right | Pain in lumbar region | None |
| Dodds[17] (1945) | 34 | F | Both | Hemorrhage. Focal necrosis in cortex | Epigastric and RUQ pain and tenderness | Had preëclampsia. Died 3 days postpartum with jaundice and hepatic necrosis |
| Edelman[18] (1945) | 61 | M | Right | Hemorrhage. Arteriosclerosis of adrenal vessels. Retroperitoneal hemorrhage | RUQ and loin pain and tenderness | Hemorrhagic adrenal removed 13 days after admission, and the patient recovered |
| Oddo[19] (1946) | 36 | F | Left | Hemorrhage forming tumor mass containing 1 qt. of blood and scattered adrenal tissue | Left costovertebral angle pain and tenderness | Patient recovered after removal of hemorrhagic tumor of adrenal |
| MacMillan[20] (1947) | 60 | M | Both | Massive hemorrhage in medulla and cortex. Thrombi in small adrenal veins | Epigastric and RUQ pain and tenderness | Hypertension |
| Burnett[21] (1948) | 23 | F | Both | Adrenals replaced by hemorrhage | — | 3 mos. pregnant. Died 2½ hr. after a spontaneous abortion |
| Arnold et al.[22] (1949) | 22 | F | Right | Hemorrhage in medulla and cortex. Recent thrombus in middle sized vein at hilus | RUQ and flank pain. Slight tenderness and rigidity | 5 mos. pregnant with active bleeding from endometrial implants |
| Berte (case 1, this report) (1950) | 58 | F | Both | Massive hemorrhage into medulla, cortex and surrounding fat | Patient in extremis; cyanotic and disoriented | Had H.C.V.D. and malignant nephrosclerosis |
| Berte (case 2, this report) (1951) | 65 | M | Both | Hemorrhage into medulla, cortex and surrounding fat, most marked on rt. Extensive necrosis due to infarction | Epigastric pain and tenderness | Also had emphysema, bronchiectasis, fibrosis and lobular pneumonia |

Note: RUQ, right upper quadrant; P.A., pernicious anemia; A.S.H.D., arteriosclerotic heart disease; chr., chronic; H.C.V.D., hypertensive cardiovascular disease.

septum into the chamber of the right ventricle; (3) diffuse atherosclerosis of the entire length of the aorta, with extensive calcium deposits associated with ulceration and rents in the intima; (4) malignant nephrosclerosis of both kidneys, with necrotic ulcerations of the outer surface from 1 to 3 cm. in diameter, and multiple pinpoint




FIG. 1. Case 2. The right adrenal (above) is markedly enlarged and completely replaced by hemorrhage. The left adrenal (below) shows a lesser degree of hemorrhage, principally in the medulla with patchy involvement of cortex.

to pinhead sized hemorrhages throughout the cortex and medulla; (5) a few small white fibrous nodules in the lateral lobes of the thyroid, without significant enlargement of the gland; (6) multiple small, pedunculated fibroids of the uterus; (7) multiple small, pinpoint sized hemorrhages throughout the mucosa and serosa of the stomach and small intestine, with a few similar hemorrhages in the mesentery of the

small intestine; (8) congestion of the spleen and liver, with slight fatty metamorphosis of the liver on microscopic section. The remaining findings, including examination of the brain, were unrevealing.

*Case 2.* A 65 year old white male was admitted to the hospital in February, 1951, complaining of weakness and dyspnea. On a previous admission (July, 1950), a diagnosis of bronchiectasis and pulmonary fibrosis was made. Significant physical findings revealed a dyspneic and cyanotic patient with blood pressure of 120/70 mm. of Hg and pulse of 80. Numerous coarse and fine râles were heard posteriorly over both lung fields. Roentgenogram of the chest was indicative of widespread pulmonary fibrosis, with emphysema and areas of calcification in the upper lung fields.



FIG. 2. Case 2. Left adrenal (×30). There is extensive necrosis and hemorrhage throughout the medulla and cortex. Marked hemorrhage extends through the capsule and into the peri-adrenal fat as seen above on the right.

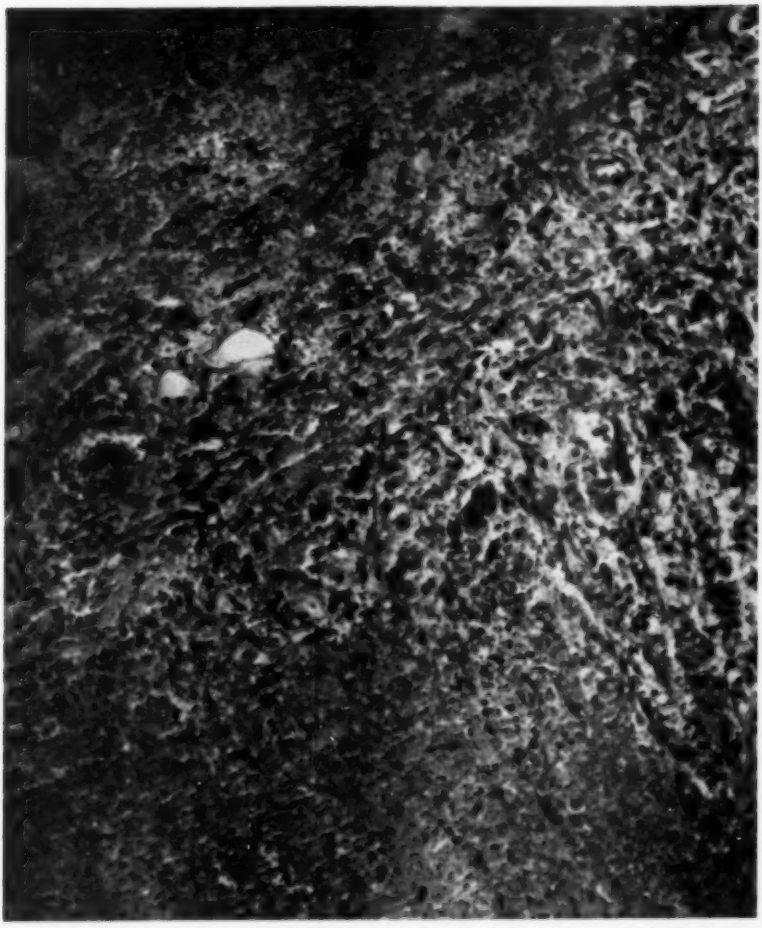


FIG. 3. Case 2. Left adrenal (× 100). Only small islands of cortical cells remain between areas of necrosis containing red blood cells and scattered lymphocyte and polymorphonuclear cells. Fresh hemorrhage can be seen extending through the capsule into the peri-adrenal fat tissue.

Erythrocyte count was 5.8 million, with 26,000 white blood cells per cubic millimeter. Blood cultures and repeated examinations of the sputum for acid-fast bacilli were negative.

On the fourth hospital day the patient suddenly developed severe epigastric pain without nausea or vomiting. The temperature rose to 103° F. but returned to normal within a few hours. There was marked tenderness over the whole upper abdomen, most marked in the epigastrium. No rebound tenderness was evident, and slight muscle spasm present was believed to be not involuntary. A surgical consultant saw the patient and did not feel that the findings in the abdomen indicated a surgical

emergency. The patient continued to complain of intermittent epigastric pain for the next eight days. On the twelfth hospital day he suddenly developed an acute episode of respiratory distress and died five minutes later.

At postmortem examination the body was poorly nourished, with moderate clubbing of the fingers and multiple tattoo markings on the skin. No petechiae or evidence of external hemorrhage was noted. The principal pathologic changes were confined to the adrenal glands. The right adrenal was markedly enlarged and dark red. It measured 6 by 5 by 5 cm. On section, the entire gland was replaced by a partly fluid blood clot. Only a few small islands of grossly recognizable adrenal cortex remained. The left adrenal was moderately enlarged and, on section, the medulla was destroyed by hemorrhage. The cortex was compressed and partially replaced by expanding blood clot. No free blood was found in the peritoneal cavity. The right adrenal was entirely filled with blood clot, and microscopic slides could not be made satisfactorily. Microscopic sections of the left adrenal gland showed almost complete destruction of medulla and cortex by expanding hemorrhage containing well preserved red blood cells. In addition to hemorrhage, a large area of necrosis with ghost cells was present in the center of the medulla. Areas of hemorrhage extended into and through the capsule. The surrounding fat showed a subacute inflammatory reaction and hemorrhage. The walls of many of the large veins within the medulla were necrotic. Although infarction of the adrenals seemed to be present, no definitely organized thrombus could be seen. Within the veins there was eosinophilic staining matter containing red cells and leukocytes. This may have represented a fresh thrombus, but the latter may have been secondary to the adjacent necrosis. The gross and microscopic findings in the adrenals of this case are illustrated in figures 1, 2 and 3, respectively.

Additional lesions were confined principally to the lungs, and included obliterative fibroadhesive pleuritis on the right, marked bronchiectasis of the right lower lobe, moderate bronchiectasis of the right middle lobe and left lower lobe, emphysema of the left upper and lower lobes, lobular pneumonia of the right upper and lower lobes, and calcification in both upper lobes. In addition to the latter, interstitial fibrosis and suppurative bronchiolitis were seen on microscopic section. The epicardial surface of the heart was smooth and glistening except for a 2 cm. fibrous plaque on the posterior surface. Microscopic sections revealed hypertrophy of myofibrillae with focal areas of degeneration in the papillary muscles. Moderate atherosclerotic plaques with some calcification and no ulceration were present in the aorta. Gross and microscopic examination of all other organs revealed either normal or insignificant changes. The brain and spinal cord were not examined.

## Review of the Literature

Spontaneous adrenal hemorrhage has occurred almost equally in the sexes, there being 11 male and 13 female patients reported. The age incidence was widespread, varying from 17 to 74. The hemorrhage was bilateral in the majority (17 cases). In six cases it was unilateral, occurring on the right side in five cases. In only two reports [18, 19] was operation performed with recovery. In each case the hemorrhage was unilateral, and the complete gland and hemorrhagic tumor were removed. The case reported by Oddo [19] was unique in that approximately one quart of blood was present as a tumor mass in the left adrenal area. In six cases adrenal hemorrhage occurred with pregnancy or following delivery or abortion. In one, carcinoma of the lung was present without metastatic involvement of the

adrenals. Two reports gave a past history of syphilis that had been treated. Hypertension was present in four patients. In one, hemorrhage occurred 11 days following a burn, pneumonia was present without septicemia in two cases, and in four no associated disease was mentioned. The remaining cases were associated with varying conditions, as noted in table 1.

A review of the abdominal signs and symptoms in these 24 cases indicates that epigastric pain is the most frequent complaint, occurring in nine cases. In four the pain was in one or both upper quadrants of the abdomen only. Two cases complained of generalized abdominal pain, and in three pain was confined to the lumbar or costovertebral area. No specification of pain was made in six cases. Frequently the pain radiated to other portions of the upper abdomen, flanks and back. Tenderness was almost always present over the site of the pain, and spasm, although frequent, was not a consistent finding. In general, the pain was usually bearable but severe and was made worse by motion. Localized hyperesthesia could be found. As the disease progressed, pallor, prostration, drop in blood pressure, cyanosis, nausea and vomiting, and finally shock developed. Fever and leukocytosis were very frequent findings. In contrast to the classic Waterhouse-Friderichsen syndrome, purpura was usually absent.

In reviewing the pathologic findings in the adrenals involved, it is noted that thrombosis in adrenal veins was described in seven cases. Hemorrhage extended into the periadrenal fat tissue in six, and intraperitoneal hemorrhage was noted in two. Arteriosclerosis of the adrenal vessels was described in one case. There was no detailed description in three cases, and the remaining reports indicated gross hemorrhage within the medulla, which was sometimes in a partly liquid state. Expansion of the hemorrhage frequently involved the cortex and capsule with associated cortical necrosis.

## Discussion

The adrenals are among the most vascular organs in the body. Classically three arteries to each gland have been described, which immediately break up into numerous capillaries intimately associated with the cortical cells. Drainage is into sinusoids in the medulla which empty into a single adrenal vein. The latter vein drains into the inferior vena cava on the right and, on the left, into the left renal vein or sometimes into the left inferior phrenic vein. Recently, however, a study of 400 autopsies by Anson et al.[23] showed that there may be up to 50 arteries to each adrenal. This fact, plus the consistent finding of a single adrenal vein, makes the gland particularly vulnerable to the frequent occurrence of venous thrombosis, as has been suggested in the cases reported herein.

Regarding the etiology of adrenal hemorrhage, the latter may be divided into four groups: (1) Involution or destruction of gland substance. The former may occur in the newborn as a consequence of degeneration of the androgenic zone in the cortex with intense hyperemia, or probably as a

result of hormonal influence in the postpartum period, when the cortex becomes less compact and rupture of vessels may occur. Tumors and infection may incite hemorrhage by destruction of gland substance. (2) Damage to the wall of the capillaries, which may occur with convulsions, toxemia, trauma, septicemia, arteriosclerotic changes, hypertension and bacterial emboli. (3) Generalized hemorrhagic diseases, including hypoprothrombinemia and the blood dyscrasias, which can produce parenchymal hemorrhage. (4) Thrombosis of the adrenal vein with infarction, which may be primary or idiopathic, or secondary to associated local disease, as regional suppuration.

From the pathologic point of view, there are three groups of adrenal hemorrhage: (1) Hemorrhage involving the entire gland, which converts it into a blood sac by complete replacement. (2) Hemorrhage that is largely confined to the medulla and is surrounded by cortex. (These two varieties of hemorrhage are usually associated with thrombosis of adrenal vein and infarction, and the resulting hemorrhage may extend into the retroperitoneal space or into the peritoneum, as is borne out by some of the case reports described.) (3) Scattered small hemorrhages occurring within the gland substance, which are noted in acute infections but are usually not the direct cause of death unless extensive gross hemorrhage ensues.

There has been an increasing number of cases of spontaneous adrenal hemorrhage of the type specified in this paper reported over the years. As noted in table 1, during the first quarter of this century four cases were reported, whereas 20 cases were uncovered during the second quarter, with an increase in number with each decade. As the awareness of this disease becomes more apparent pathologically, an increasing interest in the clinical diagnosis of adrenal hemorrhage is stimulated. There seems to be no doubt that this condition can simulate an acute abdominal emergency. It is noted that pain is almost always present and is usually epigastric. With unilateral hemorrhage, the pain may radiate to or be in one of the upper quadrants on the same side as the hemorrhage. True muscle rigidity may or may not be present. With the blood picture and other clinical findings, adrenal hemorrhage must be differentiated particularly from such conditions as acute pancreatitis or perforated peptic ulcer. In view of the two cases of Oddo and Edelman that underwent successful operation, a positive approach may be entertained when a diagnosis of massive unilateral spontaneous adrenal hemorrhage is suspected.

## Summary

A review of the literature concerning spontaneous adrenal hemorrhage in the adult apparently not due directly to infection, septicemia, neoplasm or trauma of the adrenals revealed 22 cases. To these, two new cases are added. Both latter cases had bilateral adrenal hemorrhage. One was associated with infarction of the adrenals and the other with hypertension and

malignant nephrosclerosis. A discussion is offered based upon an analysis of these 24 cases. In addition, spontaneous adrenal hemorrhage is briefly reviewed from the anatomic, etiologic, pathologic and clinical points of view. Since this disease is being recognized with increasing frequency as a pathologic entity, clinical interest should be stimulated regarding spontaneous adrenal hemorrhage and its differentiation from other acute intraabdominal diseases.

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# MOTILITY OF THE SMALL INTESTINE DURING EMOTIONAL REACTIONS *

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There have been only a few studies of the effect of emotion on the small intestine. These have not produced consistent results. Cannon was one of the first to investigate the subject.[1] He states: "The kneading movements of the small intestine cease whenever the observed animal shows signs of emotional excitement." Cannon does not specifically describe how he induced the emotional excitement that led to suppression of intestinal motility, but he does discuss the conditions under which he noted absence of gastric motility, which would appear likely to be the same. He described this absence of motility in young male cats, who were restive and excited when fastened to an animal holder, or in cats who were distressed when he covered their mouths and noses with his fingers to interfere with their breathing.

We could find no experimental studies of the effects of emotion on the small intestine in man to compare with Cannon's work in animals. We did find several papers in which the authors reported observing changes in small intestinal motility that they attributed to emotional causes. It was increased motility and spasm, however, that were attributed to emotional disturbance, rather than decreased motility as observed by Cannon. For several days, Weeks [2] was able to observe an Arab's small bowel which had been left exposed on the abdominal wall because of difficulties at operation. He reported seeing greatly increased peristaltic activity after a number of other injured yelling Arabs were admitted to the ward. Martin [3] studied 27 patients who showed barium remaining in their small intestines 14 hours after it had been administered. (In most other patients no barium was left in the small intestine after six hours.) Martin felt that in 15 of these 27 cases the delayed emptying that he saw was due to spasm of the terminal ileum. He presented roentgenograms showing the spasm of the ileum, and indicated that he felt it was due to emotional distress. Martin also reported a case in which operation was performed for small intestinal obstruction, but there was only spasm of the small intestine found at laparotomy. Heyer [4] reviewed the data on several patients who had been subjected to operation for small intestinal obstruction and found to have only areas of spasm of the

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small intestine. He also considered that the spasm was the result of emotional disturbance.

In studies of the effect of emotion on the stomach and colon some observers have noted increased motility and others decreased motility as a result of emotion. Thus, while Wolf and Wolff [5] noted that anger and resentment led to hypermotility in their case of gastric fistula, Crider and Walker [6] noted decreased motility during anger and resentment in a woman with a gastric fistula. Almy and associates [7] stated that some subjects when under stress showed hypermotility of the colon, others, hypomotility, depending upon their emotional reaction. Wener and Polonsky [8] described somewhat similar findings in their study. These two reports differed from Cannon's conclusion that there is general hypomotility throughout the gastrointestinal tract in animals during pain, anger or fright.

As there were so few studies of the effect of emotion on the motility of the human small intestine, and as some of the observations on this and on other portions of the digestive tract appeared contradictory, we felt that further studies would be worth while.

## Method

Patients from the gastrointestinal wards were studied. They had a variety of conditions: peptic ulcer, amebiasis and functional gastrointestinal disease manifested by diarrhea, vomiting or pain.

To obtain the record of intestinal motility, a Miller-Abbott tube was passed, under fluoroscopic control, into the duodenum or, more frequently, into the upper jejunum. A diagram was drawn on the record indicating the position of the tube at the time of the final fluoroscopy before testing. The balloon of the Miller-Abbott tube was filled with 10, 15 or 20 c.c. of air and then connected to a tambour. The contractions of the intestine upon the balloon forced air into the chamber of the tambour, elevating the lever arm, which recorded on a kymograph. A record of intestinal motility described in ink on glazed paper was thus obtained. It showed a basal level above the level of the lever arm at rest, which was interpreted as due to tonus within the small intestine. There were rapid small waves occurring at rates of nine to 14 per minute which were considered segmenting waves. There were also slower, larger waves, often taller and with a broad base, one-half to two minutes in duration, which were considered peristaltic waves. The smaller waves were sometimes superimposed upon the larger waves. There were also "spasms" in which the basal level rose markedly, usually to the upper limit of the previous contractions, and remained elevated for five to 15 minutes, and there were superimposed segmenting waves of wide amplitude. Following these "spasms" there was a variable period during which peristaltic waves were absent.

In order to have a simple system of grading our records, we arbitrarily classified the large waves 1 plus to 4 plus on the basis of frequency, small

waves 1 plus to 4 plus on the basis of amplitude, and tone 1 plus to 4 plus on the basis of height above the base line. In tabulating these values for a given period of time, we have had to estimate a value for the period as a whole because of the rapid changes from moment to moment.

To elicit emotional reactions in the patients we used an interview technic. The patient was usually interviewed by a psychiatrist several times before the actual test. When the Miller-Abbott tube was in place, the patient was interviewed by the same psychiatrist with no other person present. Knowing the patient, the psychiatrist planned to lead the interview at times into areas of conflict, and at other times to topics that were apparently not disturbing, although sometimes no attempt was made to direct the interview. The record of intestinal motility obtained while the patient was discussing nondisturbing topics was to be used as a control for comparison with the record obtained while he was discussing disturbing topics.

Where possible, records were also obtained with the patient resting alone before and after the interview.

After the study, the patient was fluoroscoped to check the position of the tube, and a diagram indicating this position was made on the record.

The psychiatrist attempted to determine the emotional status of the patient by noting the patient's facial expression, his movements, his statements and his manner of speaking. When the patient told the examiner of a specific emotion this was noted. The patient was also asked how he felt at different times during the interview. Symptoms such as pain, nausea or other distress were also recorded.

In some cases a record of respiration was taken along with the record of intestinal motility. This record was obtained by fastening a pneumograph around the lower margin of the chest and connecting it to a tambour, which then recorded above the record of intestinal motility. This respiratory record was useful in recognizing deep breathing, breath holding, talking, coughing, retching or belching, all of which have at times altered the pattern of intestinal motility records. When a pneumograph was not used these alterations in respiration were indicated by the interviewer on the record of intestinal motility.

## Observations

We obtained one or more satisfactory records of the intestinal motility during an interview in 20 patients, and during these interviews observed 34 emotional reactions. A definite change in intestinal motility accompanied seven of these. In the remaining 27 there was either no change or a variation in motility of dubious significance.

Two of the cases that showed changes in motility during an emotional reaction have been illustrated: Case 5, as can be seen in figure 1, showed a pattern of intestinal motility during interview C different from those during his other three interviews. About an hour before interview C he had been




FIG. 1. Records of intestinal motility during four interviews of case 5.

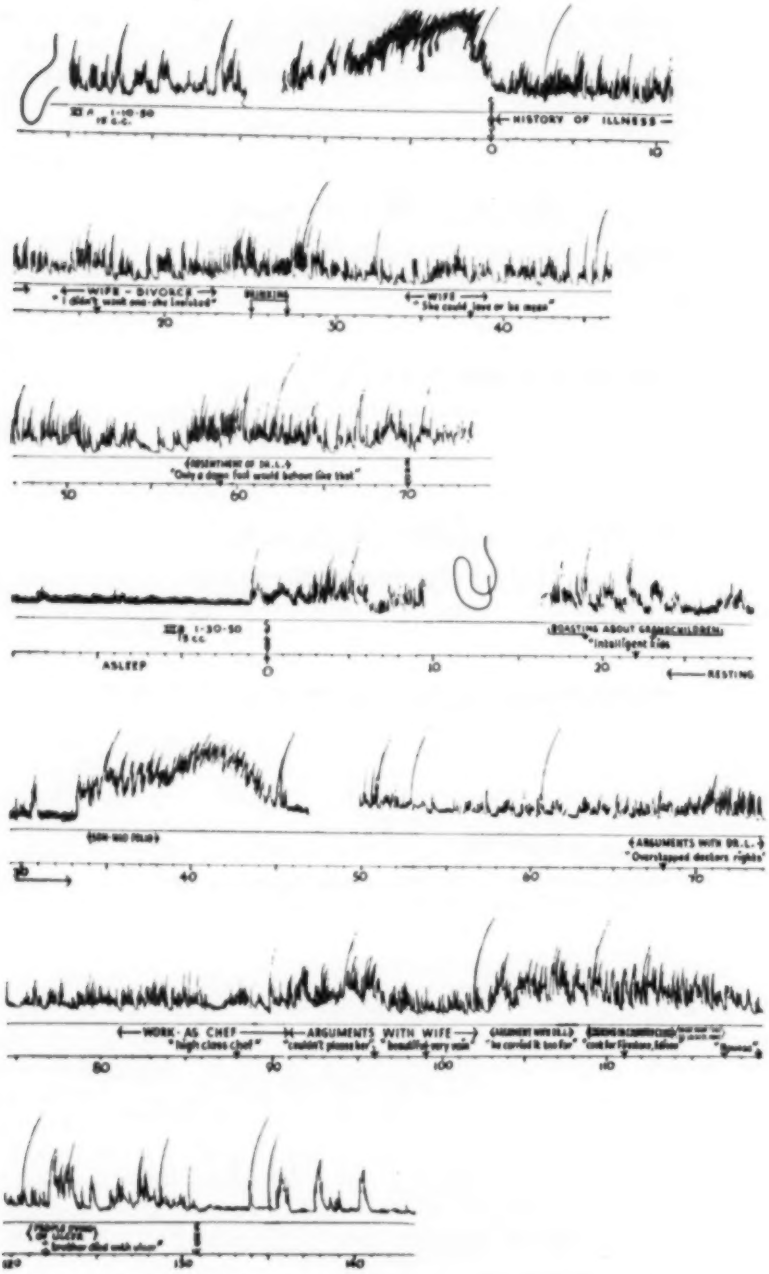



FIG. 2a. Records of intestinal motility during two interviews of case 6.

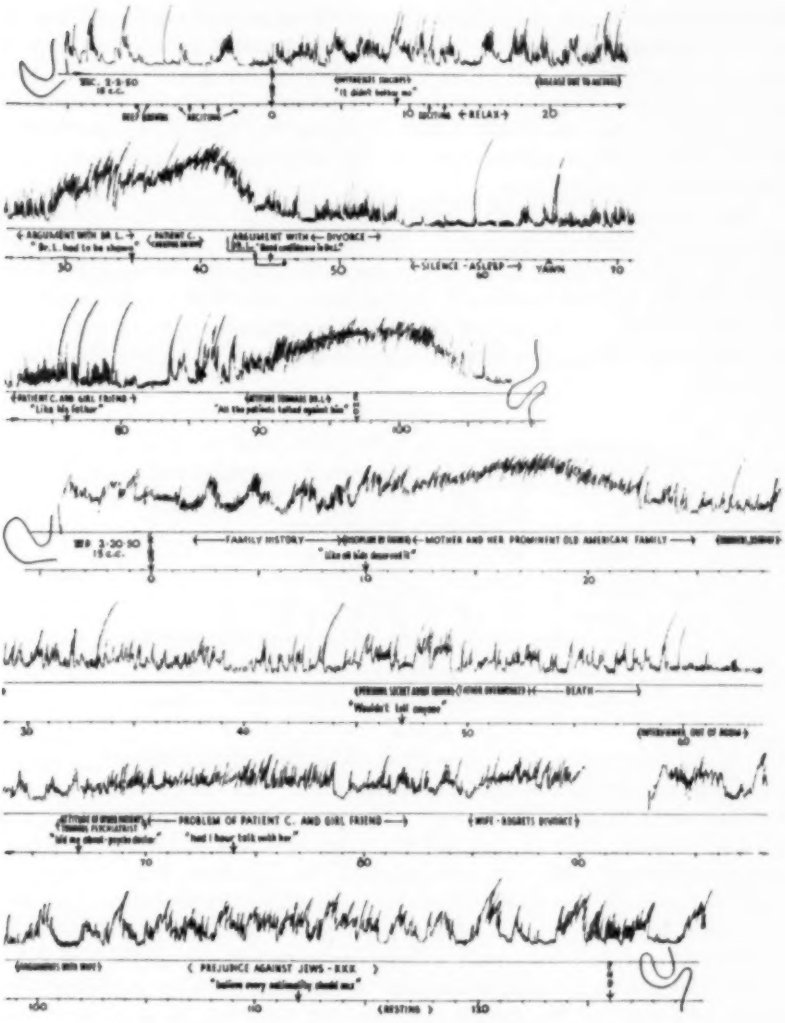



FIG. 2b. Records of intestinal motility during two interviews of case 6.

given a ticket for parking which he felt he did not deserve. For the first 20 minutes of the interview he talked about this incident and about other difficulties he had had with policemen and irritating people. As he did so, he became angrier and angrier; at the same time, the tone of his intestine rose progressively. As he told of his attempts to control his anger at the "cop" he retched repeatedly. Then, when an attempt was made to soothe

the patient, he did talk of the difficulties of the policeman's job, and how he was not unreasonable with "cops." He then recalled another incident in which he had been insulted by an officer, and retched again. He was then deliberately led to discuss the air races, which was felt to be a more neutral topic, but even here he finally began to discuss the parking possibilities at the air races. His intestinal tone did not return to its usual level at any time during the interview.

The second case to show a definite change in intestinal motility during an emotional reaction was case 6. During the four interviews of this patient illustrated in figures 2a and 2b, it can be seen that he discussed his ward physician, Dr. L., five times, and four of these times had an associated rise in intestinal tone. The patient resented his ward physician intensely, and indicated this in comments about the doctor that were at times rather bitter,

TABLE I

Intestinal Motility During Different Emotional Reactions

| EMOTIONAL REACTION | NUMBER OF EXAMPLES | PERISTALSIS | | | | TONE | | | | "SPASM" | COULD NOT BE MEASURED |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | + | ++ | +++ | ++++ | + | ++ | +++ | ++++ | | |
| ANGER | 18 | | 3 | 8 | 4 | | 6 | 5 | 4 | 2 | 1 |
| ANXIETY | 10 | 1 | 2 | 3 | 4 | | 5 | 4 | 1 | | |
| WEEPING | 3 | 1 | 1 | | 1 | | 3 | | | | |
| FEAR | 2 | | 1 | 1 | | | 1 | 1 | | | |
| PLEASURE | 3 | | 1 | 2 | | | 2 | 1 | | | |

Average for all the records in the entire study with this arbitrary system of grading: peristalsis about ++; tone about ++

as, "Only a damn fool would behave like that." The resentment was over the physician's handling of his case. The patient had been admitted for nausea and vomiting that he had had for years and that had recently become more troublesome. He felt, and had told the physician, that one food he could not tolerate was milk. Yet the ward physician first gave him milk and cream hourly and, when this did not prove effective, placed him on a constant drip of milk and cream, in spite of the patient's protests.

We did not find a distinct pattern of intestinal motility regularly associated with each of the specific emotions we observed, as is evident from table 1. We did, however, have the impression that tone was usually increased during anger. This increased tone was observed during short periods of anger that occurred in the course of an interview, and during the entire interview of two patients who were persistently hostile. On the other hand, the three patients who cried or were tearful during their interviews showed a tendency towards hypomotility. There was not even a suggestion of a common pattern among the patients who were anxious or those who were apparently enjoying the interview.

A few observations pointed to the possible importance of the intensity of the emotional reaction in determining the intestinal motility response. Thus, of the 13 patients who became angry during their interviews, only three showed a definite change in intestinal motility, and at least two of these seemed more angry than the remaining 10. Yet in a fourth patient, who

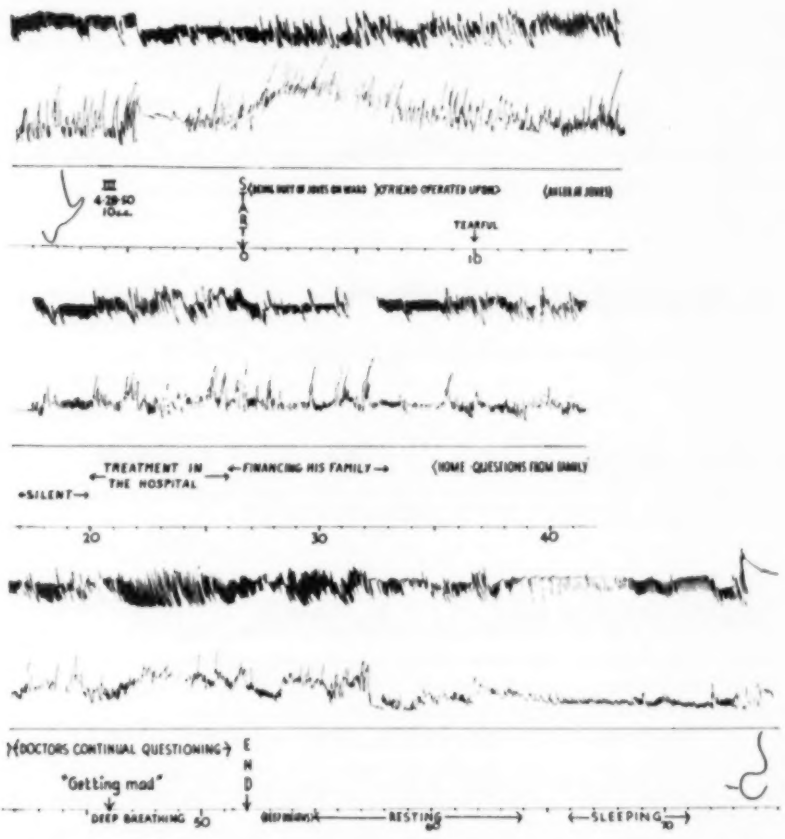



FIG. 3. Record of respiration and intestinal motility during an interview of case 3.

was intensely and definitely angrier than any of the other patients, including these three, findings were different. Although his record was hard to evaluate, he seemed to show a suppression of wave motion rather than the usual rise in tone. The record on this patient is illustrated in figure 3. Toward the end of the interview this patient complained of the way his family always questioned him when he went home. Then he complained of the way the

examiner asked questions, the same questions over and over; he began to tremble, breathe deeply, and clench and unclench his fists as he told the examiner, "I am getting mad." His tone appeared to rise at this time, but when his deep breathing stopped his tone dropped. To determine whether the deep breathing might have caused this apparent rise in tone, we asked him to breathe deeply again for a minute or so. There was again an apparent rise in tone. We therefore could not be certain of the pattern of the patient's intestinal motility during the period when he was breathing deeply in anger; but it seemed likely that we might have seen the suppression of motility and

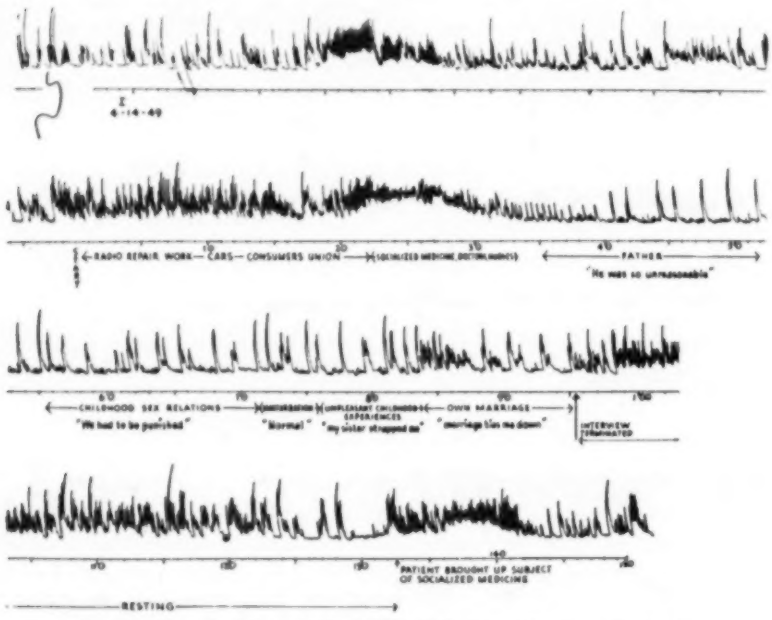



FIG. 4. Record of intestinal motility during an interview of case 1.

lowered tone during this period of intense anger that we saw after it, if the deep breathing had not altered the record.

Often during interviews patients discussed material that we thought might be disturbing to them, yet they showed no overt evidence of emotion. During these periods we saw changes in intestinal motility on only a few occasions and then were not sure the changes were significant. In one case, however, our findings were suggestive, as illustrated in the record of patient 1, presented in figure 4. During the first part of his interview this patient discussed radio repair work, cars, consumers' union and socialized medicine without evident emotion. The only notable change in the record was a rise in intestinal tone during the discussion of socialized medicine. In the re-

mainder of the interview the patient discussed a number of things that had been disturbing to him: his father's beating him or embarrassing him, or mistreating his mother; an episode where he was accused of a sex offense as a boy; masturbation, which he stated he now accepts as normal, although formerly it had produced feelings of guilt; the fact that he missed affection as a child and hence could not love now; his marriage, which he now resented because it tied him down, because he was obliged to live with in-laws, and because his wife was unduly concerned with trivial things. During this entire period the tone and peristalsis showed no marked change and were like the pre-interview period. Then, after the interview had been over for 37 minutes, the patient again brought up the subject of socialized medicine, at which time there was again a rise in intestinal tone. The examiner did not recognize any apparent emotional reaction at this time. The fact that this patient spontaneously brought up the subject of socialized medicine, long after the interview was over, suggested that discussion of this topic with a physician was more significant and disturbing to him than was apparent. If so, the rise in intestinal tone on both occasions that he discussed the subject may have been significant.

It was interesting to us to note that each of three patients on whom we had four or more studies (cases 4, 5 and 6) showed a different response during his interviews. Case 4 developed a definite emotional reaction several times: he became angry twice, anxious twice and, on one occasion, cried. He did not show a striking change in his intestinal motility pattern during any of these emotional reactions. Case 5 became angry only once and then showed a definitely elevated intestinal tone. He showed no other clear-cut emotional response, but his interviews seemed to be interrupted or terminated by vomiting when he came to a particularly disturbing topic. Case 6 was usually calm but would become resentful when discussing his ward physician, and at these times would show a rise in intestinal tone.

A number of our 20 patients did develop one or more of their symptoms during the interviews. Nausea, retching and gagging, for example, were seen in four cases and had been admitting complaints in three of these cases. We could not attribute much significance to nausea and vomiting in a patient who had an intestinal tube irritating his throat, yet it was interesting that the patients who had nausea and vomiting during the study were usually the ones who had previously presented it as a symptom. Abdominal pain developed during the interviews in three cases. They had also had this symptom as a presenting complaint. One patient stated that his stomach was "growling" during the interview, as it often did when he was "nervous"; another complained of bloating, again a symptom he had had before.

These symptoms often appeared when the patient was discussing material involving a conflict, but he was not necessarily showing overt evidence of emotion. Case 5 illustrated well the presence of gagging and vomiting when conflictual data were discussed. He did not usually show evidence of emotion at these times, although during interview C, when he retched repeatedly,

he was also obviously angry. A number of other patients appeared anxious at the time they developed their symptoms. Thus, one patient retched and appeared anxious when he was urged to discuss his unpleasant war experiences; and four patients who were apprehensive about the test procedure presented a variety of complaints: pain in the abdomen, "stomach growling," "stomach bubbling" and "gas pains and bloating."

Usually we could find no correlation between these symptoms and the motility of the portion of the small intestine being studied, although it is possible there were changes in motility in other portions of the gastrointestinal tract. However, there was one patient who, the observer felt on the two occasions that he studied him, showed exacerbations of abdominal pain as each successive peristaltic wave was recorded. It was also interesting that in three cases who retched repeatedly, peristalsis was quite active, which is consistent with the finding of Oppenheimer and Mann [9] that there is increased upper small intestinal motility prior to vomiting.

## Discussion

During our study we did find evidence of a relationship between intestinal motility and emotion but we also encountered a number of difficulties and possible sources of error that made it impossible for us to evaluate a large part of our data and made us cautious in accepting even our apparently definite findings. As a great many studies similar to ours are being presented in the literature, and as readers who are not actually working in this field may not be aware of the many possible sources of error in this type of study, we felt that we would present and illustrate some of those that we had noted. We have divided them into two main groups: those related to the evaluation of the emotional status of the patient, and those related to the interpretation of the record of intestinal motility.

In the first group there were three problems, the first of which was to decide exactly which emotion a patient was experiencing. We had a large group in which we could recognize no specific emotion but could determine only that the patient was anxious. We had others in whom we could recognize that there was a specific emotion but could not decide which of several terms best described it, for we found it difficult to distinguish between emotions, particularly those which are quite similar. Thus we were uncertain whether to call case 6's reaction when discussing his ward physician hate, resentment or anger. We had still another group of cases in which the patient appeared to experience several emotions at the same moment or in rapid succession, and it was difficult to determine which emotion predominated. Case 4 presented this problem in interview A: he cried as he talked of his unit's tanks shelling their own man; then he talked of wanting "to kick the guy using the field glasses in the ass" for neglecting his duty and letting this happen; then he blamed himself, as "Good Luck Guy in the outfit" for not being there. Here were sadness, anger and remorse, and it was

hard to say which predominated. The patient indicated later in the interview that he had difficulty himself in analyzing his feelings. He talked of soldiers who plundered German farms, and of one soldier who threatened to bayonet a German woman; then he said, "I feel sad, I feel disgusted with myself; I guess what I feel is guilt because that was my outfit, and I should have been up there."

The second problem was to determine the intensity of the patient's emotional reaction. We felt that an accurate measurement might be important, as we had some evidence that there was a different reaction with different intensities of emotion. As there was no exact method available, however, we had to depend on an estimate by the interviewer.

Obtaining a period when the patient was relaxed, for use as a control, was our third problem. We did not feel that the resting period before the interview could be considered a period free of emotional tension, for some patients were uncomfortable because of the presence of the tube, and many had disturbing thoughts and fears about the test itself. We learned of some of these thoughts from their comments during interviews. One patient was afraid that if he vomited during study the "ball" on the end of the tube would not come out; another patient wanted to know if our apparatus was a lie detector; others feared the examiner's questioning, and still others felt they were "guinea pigs."

We tried to get patients relaxed during the interview itself by leading them to discuss topics that we felt would not be disturbing to them and might even be pleasant. We were apparently successful in this in a few cases, but we also had patients who seemed to be enjoying a discussion yet probably were not. Thus case 5 in interview B talked with apparent self-satisfaction for several minutes about his success in his studies, then admitted that he was actually failing. There were also some patients who could not discuss any subject without becoming emotionally involved. Patient 14, for example, when the weather was mentioned, said, "It's hot and I feel restless," and when the subject of television was brought up, said "My father is too stuck up to pay attention to my television set."

When we found a patient relaxed it was usually during the post-interview period, but many were not relaxed even at this time. Some were probably still thinking about the interview, as seemed likely in case 1 who, 37 minutes after interview was over, brought up one of the topics that had been discussed. Others may have been anxious to have the tube removed.

We had the difficulties in the evaluation of the emotional status that have just been enumerated even in patients who had undergone many hours of psychiatric study. As a result of such study, we were often able to anticipate which topics would be most disturbing to a patient and to recognize his ways of showing emotion; nevertheless, there would still be periods in the test interviews when we could not evaluate his emotional status. We felt that a still more lengthy individual study of the patient would have been of

help in overcoming some of these difficulties, but we were also impressed with the need for the development of more definite criteria and more objective methods than are now available for distinguishing the individual emotions and for grading their intensity.

The second main group of problems dealt with the interpretation of the kymographic record of intestinal motility. They were concerned with the differentiation of physiologic variations in intestinal motility and artifacts, due to our method of recording, from significant changes in intestinal motility.

As there were frequent changes in the intestinal motility of patients who were apparently lying quietly at rest, we could not be certain that a change in the pattern of intestinal motility during an emotional reaction was actually due to the emotional reaction.

The pattern of the records of intestinal motility was at times so irregular that it was difficult to analyze. Certain large waves that are seen in records of intestinal motility have been shown by Ingelfinger and Abbott [10] and by Chapman and Polazzo [11] to be associated with peristaltic movements. It is therefore important to identify these waves in tabulating the motility of the intestine at any given time. Yet, as can be appreciated by looking at some of the illustrated records, there were times when it was impossible to recognize these waves. It was also impossible in some segments to recognize a basal level of the wave pattern to use in measuring intestinal tone. Further, there were periods when there was a rise in this basal level that could have been interpreted as due to a rise in intestinal tone when actually it was due to an increase in intra-abdominal pressure. Thus, in the study of case 3, there was a period when there was a rise in the basal level that was due to increased intra-abdominal pressure secondary to rapid deep breathing.

The diminished motility often noted at the end of a study might at first be considered as due to the patient's relaxation as the interview was completed. Yet here there were two other possible factors that had to be taken into consideration: (1) There tended to be a diminution in intestinal motility as the tube was allowed to remain in a given area over a period of several hours.[12] (2) Motility tended to diminish progressively as the tube passed down the small intestine.[13] In several cases the tube did progress down the intestinal tract to some extent, as indicated by fluoroscopic examination at the end of the study. In other cases, although there was no change in the position of the tube on fluoroscopy, the small intestine may have crept up on the tube, so that the balloon was actually recording from a lower level of the intestine.

It should also be mentioned that Brody and others [14] have pointed out that, with the balloon-tambour method of recording intestinal motility that we used, pressure changes in the intestine are not recorded with complete accuracy. However, inasmuch as we were interested in gross patterns and gross changes in intestinal motility, we felt that this source of error was not of major importance in our study.

Finally, it is important to realize, in evaluating this study, that motility was being recorded only from a segment of intestine about two inches long; and motility in this small segment may not at times have been representative of the motility of the small intestine as a whole. In fact, the partially inflated balloon from which recordings were obtained may have acted as a continuous stimulus to the area of intestine within which it lay, so that this area was more active than the adjacent areas.

We were impressed by these sources of error throughout our work. We felt that other investigators doing this type of study must face the difficulties, and this could well account for the fact that they obtained different answers to the same problem. Until there is a more exact, objective method of measuring a patient's emotional reactions, it would seem to us that all studies of this type should be accepted cautiously and tentatively.

## Summary and Conclusions

1. The motility of the small intestine was recorded by the balloon-tambour method in 20 patients during psychiatric interviews in which emotional reactions were elicited and evaluated.

2. Difficulties and sources of error in the evaluation of the emotional status of the patient and in the interpretation of the records of intestinal motility were noted, and the extent that they limit the accuracy of this type of study was discussed.

3. Significant emotional reactions were observed on 34 occasions. During only seven of these was there simultaneously a definite change in intestinal motility.

4. No characteristic pattern of intestinal motility was consistently associated with any specific emotion, although there seemed to be a tendency for anger to be associated with increased tone.

5. A number of patients developed symptoms during the interviews similar to their admitting complaints, but these usually could not be correlated with any change in the motility of the portion of the small intestine being studied.

### Acknowledgment

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# FAR EAST COMMAND CONFERENCE ON EPIDEMIC HEMORRHAGIC FEVER: INTRODUCTION *

By Joseph H. McNinch, Colonel, MC, Chief of Preventive Medicine, Far East Command

Today we have before us for discussion a disease entity which has created intense interest among both medical and lay personnel in the Far East Command. During the month of June, 1951, there were admitted to the United States medical installations in Korea several patients with an acute febrile disease presenting a combination of symptoms and signs not previously encountered among United Nations personnel in Korea. The symptoms included malaise, weakness, chills, fever, headache (especially retrobulbar ache), blurred vision, nausea and vomiting. These symptoms were associated with manifestations of hemorrhagic diathesis: petechial rash, marked injection of the conjunctivae, hematuria and hematemesis. Jaundice was not present in any case. Examination of the blood revealed a leukemoid reaction, with white cell counts ranging from 20,000 to 75,000 per cubic millimeter. In some cases there was a reduction in the number of blood platelets. Examination of the urine showed in all cases a severe albuminuria without other constant abnormalities.

The first patients seen gave a history of malarial attacks with recent treatment with the drug *chloroquine*, and for a time the possibility of drug sensitivity was given serious consideration. The admission of additional patients with the same clinical syndrome but without a history of chloroquine medication resulted in the early abandonment of this tentative diagnosis. In the meantime, some patients with conjunctival injection developed frank subconjunctival hemorrhages which led to consideration of leptospirosis (Weil's disease) as the most probable diagnosis. The signs, symptoms and course of the disease being seen were consistent with those of leptospirosis, except that jaundice was absent in every case. It was well known that many cases of leptospirosis do not develop visible jaundice, but it is unusual for none to do so. Immediate diagnostic tests were instituted in an effort to confirm or refute this diagnosis. The blood of patients was examined directly under the microscope in an effort to find the causative organism; laboratory animals known to be susceptible to leptospirosis were inoculated with blood and urine of patients and with tissues from fatal cases, and the blood sera of patients were tested for specific agglutinins.

* Received for publication July 25, 1952.

The Far East Command Conference on Epidemic Hemorrhagic Fever was held in Korea in December 1951. From the numerous papers presented to this Conference and submitted to the Annals of Internal Medicine for publication, a selection was made by the Board of Editors of those which would give to the readers of this Journal a general picture of this interesting disease.—Editor.

The results of these tests were confusing. Direct examination of the blood resulted in the reporting of filamentous objects which were believed at first to be the *Leptospira icterohaemorrhagiae*. However, no inoculated animal developed a typical infection, and tests of paired sera did not show significant titers against strains of *L. icterohaemorrhagiae, L. hebdomadis A, L. hebdomadis B.* or *L. australis.* Twelve additional strains of leptospira furnished by the Army Medical Service Graduate School were used for agglutination tests, with negative results. Likewise, the gross and microscopic pathology in fatal cases failed to reveal the typical lesions of leptospirosis.

These diagnostic procedures were time-consuming, and several weeks elapsed before it was possible to know positively that this disease was not leptospirosis. Between the period June 28 and July 23, 55 cases had been observed, all from combat units of the Eighth Army. As late as July 28, medical personnel of the Eighth Army were sufficiently convinced that the disease was leptospirosis to institute a control program specifically directed against that disease.

During the latter part of July, Surgeon General George Armstrong and Major General Hume, then Chief Surgeon of the Far East Command, on an inspection visit in Korea and noting the high incidence of the leptospirosis-like disease, arranged for Colonel Arthur Long, Far East Command Consultant in Preventive Medicine, to visit Korea immediately to observe the new disease entity. Colonel Long saw patients sick with this disease in one of the Army hospitals, and conferred with medical officers treating the disease, with laboratory officers and with medical officers in units from which most of the cases were originating. He did not believe that the filamentous objects seen during microscopic examination of the blood were leptospira, and this viewpoint was supported by the concurrent observations of the same objects in the blood of duty personnel in the hospital. Colonel Richard Mason, clinical pathologist, on temporary duty in Korea from the Army Medical Service Graduate School, examined specimens of blood from patients and confirmed Colonel Long's doubts. Reports of the presence of large numbers of field rodents in the areas from which the cases were originating were confirmed.

About this time, attention was directed toward a disease which the Japanese Army had encountered in Manchuria in 1939–1941, and which was written up in Japanese medical literature. This disease, which had been known variously as Songo fever, Kokka disease, Korin fever, Nidoko disease and epidemic hemorrhagic fever by the Japanese, had already attracted the attention of U. S. Army medical officers on at least two previous occasions during the Korean conflict.

Due to the thoroughness and foresight of one or more workers who contributed to the U. S. Army technical bulletins on Korea and Manchuria (TB MED 208, 1945, and TB MED 216, 1946), this disease, which finally came to be known by the Japanese as epidemic hemorrhagic fever, was de-

scribed in both bulletins. Aware of the possibility of encountering this disease in Korea, Captain John Craig, MC, Preventive Medicine Officer of the U. S. X Corps in the fall of 1950, requested the Commanding Officer of the 406th Medical General Laboratory to obtain further information from Japanese sources. Such material was collected, but found no immediate use.

In February and March of the following year (1951), there were several cases of hemorrhagic smallpox in the Far East Command, at which time epidemic fever was considered as the possible diagnosis of the fulminating hemorrhagic disease being seen. The virus of smallpox was successfully isolated and the cases were definitely identified as hemorrhagic smallpox of the purpura variolosa type. At the same time it was deemed advisable to disseminate information which had been collected on epidemic hemorrhagic fever for the information of medical personnel of the Far East Command, and Captain Craig compiled a brief résumé which was published in mimeographed form and distributed within the Command.

It was not strange, then, that medical personnel of the Far East Command, on failing to confirm the diagnosis of leptospirosis, again considered epidemic hemorrhagic fever as the correct diagnosis.

So far as was then known, except for the U. S. Army technical medical bulletins referred to there were no other references to this disease in American or European medical literature.*

In order to learn more about the Japanese experience with this exotic disease, Captain Ralph M. Takami, MC, U. S. Army, began the collection and translation of pertinent articles in the Japanese medical literature, and also interviewed the principal Japanese medical scientists who had worked with the disease between 1941 and 1945. On August 13, 1951, a mimeographed review of the Japanese literature, supplemented by material gained from the personal interviews, was published by Captain Takami.

This publication was distributed widely in the Far East Command to acquaint medical service personnel with the characteristics of this disease, of which few had ever heard or read. Copies were also forwarded to the Surgeon General of the Army.

By the time this review was published, the number of new cases being reported each week seemed to be decreasing. Sixty-eight cases had been reported for a four week period in July, and only 16 new cases were reported during the first three weeks of August. Up to this time most cases had been treated in the 121st Evacuation Hospital in Korea, although a few patients had been evacuated to Japan and an occasional case had developed in patients evacuated to Japan for other reasons (usually for treatment of battle wounds). Except for minor differences, the clinical picture paralleled closely that described as epidemic hemorrhagic fever by the Japanese. The

* Subsequently there was received in the Far East Command a preliminary draft, "Epidemic Hemorrhagic Fever," by C. F. Mayer, December, 1951, a review of published literature on this disease, containing references to articles in the Russian literature.

gross and microscopic pathology in fatal cases was consistent with that described by the Japanese. Slides were obtained from Japanese workers for comparison, and a Japanese pathologist who had worked with the disease reviewed slides from tissues of fatal cases. Both United States and Japanese workers agreed that from the standpoint of microscopic pathology, the disease now being seen in Korea was the same as that experienced by the Japanese Army in Manchuria. However, Japanese workers claimed to have reproduced a recognizable infection in laboratory animals, and these results had not been confirmed by United States laboratory personnel.

As of September 1, 1951, the situation was somewhat confused. A disease which closely resembled leptospirosis had appeared in United Nations forces in Korea. However, various laboratory tests had failed to establish this diagnosis, and attention had been directed to a hitherto unknown disease reported by the Japanese as having attacked their troops stationed in Manchuria prior to World War II. The clinical picture and pathology of the disease attacking troops in Korea closely resembled the disease reported by the Japanese, and named by them epidemic hemorrhagic fever. Such epidemiologic data as had been collected were also consistent with Japanese reports, but actually very little such data had been collected by September 1. There was an understandable reluctance on the part of United States medical personnel to accept without question the Japanese report on the identification of a disease entity unknown to American medicine without confirmatory studies. Furthermore, the Japanese had identified the causative agent as a virus, and many American observers were sufficiently impressed by the close resemblance of the clinical picture to other diseases known to be rickettsial in origin that there was doubt as to the accuracy of the virus hypotheses. At this time the general tendency in the United States personnel seemed to be: Wait to see if the second larger peak, experienced by the Japanese and predicted by them, would occur. The answer to this question was not long delayed. In the last week in September 16 new cases occurred, and in the first week in October this number rose to 28. It rapidly became apparent that the epidemic was to have a second peak, and that it was to be much larger than the first.

During the first peak, epidemiologic, clinical and pathologic studies had been instituted to determine whether this disease was in fact epidemic hemorrhagic fever, and to acquire knowledge that would be useful in its prevention or control and in its treatment. The latter seemed to be very important, since early in the epidemic the case fatality rate fluctuated between 13 and 18 per cent. This was indeed no mild, insignificant infection which was affecting United Nations troops. During the first peak of the epidemic it had been Eighth Army policy to concentrate all cases in one hospital in Korea to facilitate clinical and laboratory studies. However, during the second peak this was no longer possible, due in part to the larger number of cases and in part to a temporary increase in the number of battle casualties received for treatment. Cases of this disease found their way into many

hospitals in both Korea and Japan. As a result, a number of medical officers in the Far East Command have had an opportunity to observe and study this disease.

The Japanese have described epidemic hemorrhagic fever as due to a filterable virus maintained in the field rodent *Apodemus agrarius* as a reservoir and transmitted to the human by the bite of the mite *Laelaps jettmari*, one of the ectoparasites of this rodent. It has never been present in Korea, either north or south, so far as the Japanese know. These concepts presented to United States medical personnel the problem of confirming, if possible, the etiology and mode of transmission as described, and determining, if possible, the extent of its distribution, the method by which it was introduced into Korea and when. Intensive attempts have been made to infect experimentally the standard laboratory animals and chick embryos, and to collect and analyze epidemiologic data. The results of the attempts to infect experimental animals have so far been negative.

The epidemiologic data thus far collected cannot be presented in detail at this time. It must be noted that this epidemic has involved combat troops engaged in active operations in Korea. Any epidemiologic study must necessarily entail a statistical analysis of incidence, strength and disposition of units and geographic data which for the time being involve security of United Nations troops. However, certain facts can be presented which are useful in arriving at a better understanding of this exotic disease.

In the Japanese experience, epidemic hemorrhagic fever occurred from May until December, with two peaks, one in May and June, a second in October and November. Sporadic cases occurred throughout the year. In the present epidemic in Korea, the first cases were reported in June and increased in number until the last week in July, after which the incidence fell off, reaching a low of four new cases during the first week in September. Throughout the month of September the number of new cases reported each week varied but remained low. By the end of the first week in October, the number of new cases being reported left no doubt that there was to be a second peak in the epidemic, and it soon became apparent that the number of cases would greatly exceed the number in the first peak. The relative spread and magnitude of the two waves are apparent from figure 1. It is likely that the difference in magnitude is exaggerated. During the first wave of cases the criteria for diagnosis were indefinite, and such criteria as had been established were known to a relatively small percentage of the United Nations medical personnel because of difficulties in the dissemination of information throughout a large composite military organization engaged in combat operations. On the other hand, it is probable that the second wave of cases was exaggerated by overdiagnosis; by October, most medical personnel, in the United States forces at least, were acutely aware of the new clinical entity and constantly on the search for new cases. Since mild cases present considerable difficulty in differential diagnosis, it is presumed that some cases of other diseases were mistakenly diagnosed epidemic hemor-

rhagic fever. As of this date (December 22, 1951), the second wave is apparently on the decline. It is of course too early to predict its future course. However, thus far the seasonal occurrence closely parallels that described by the Japanese.

The concentration of cases is shown on the map in figure 2. It is possible that this heavy concentration reflects a geographic concentration of the etiologic agent among the rodent and arthropod fauna, or concentration about one or more foci of patients sick with the disease, with person-to-person spread. Investigations thus far indicate there has been no person-to-person spread in the troops, and no case has occurred among medical personnel caring for patients sick with the disease, although precautions against such spread have been minimal in a number of hospitals. All evidence at this time seems to support the Japanese hypothesis that the disease is carried by a rodent host and spread by an ectoparasite vector. However, it is true that the epidemiology is also consistent with hypotheses which

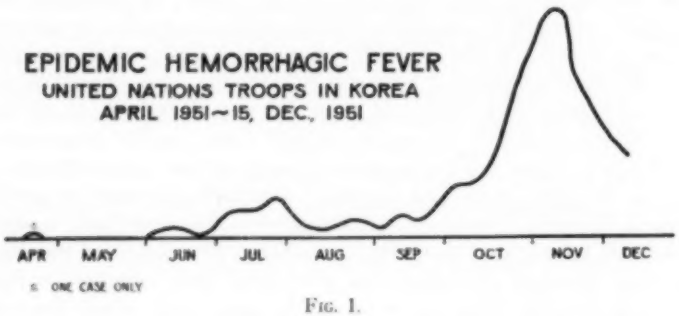



FIG. 1.

might concern hosts and vector parasites other than those described by the Japanese.

Among United Nations troops, personnel from all nations have been attacked, in numbers roughly consistent with their strength and nearness to the geographic areas involved, with perhaps the Republic of Korea soldiers as an exception. Cases have occurred among the ROK Army but the incidence has not seemed so high as in the UN troops. Whether this is more apparent than real, due to a difference in diagnostic acumen in ROK Army medical personnel, has not been determined. There appear to have been few if any proved cases among the civilian population. Here again, the minimal medical care available to civilians, especially in rural areas, may be a factor. Also, it is to be noted that most of the civilians have been removed from the most forward areas, in which the highest concentration of cases has been found.

Repeated attempts have been made to determine whether this disease existed in South Korea prior to the current epidemic, generally with unsatisfactory results. If the disease has a field rodent as its reservoir, and is

therefore primarily a rural rather than an urban disease, it is possible that cases may occur in rural Korea without medical attention. Such medical attention as was available may have been provided by personnel insufficiently trained to have differentiated this disease from other diseases with similar symptomatology, such as leptospirosis, typhus fever and relapsing fever, or even from hemorrhagic smallpox. Likewise, interrogation of local physicians and lay inhabitants was difficult, particularly since most such interrogations were made through a nonmedical interpreter. At this time, it

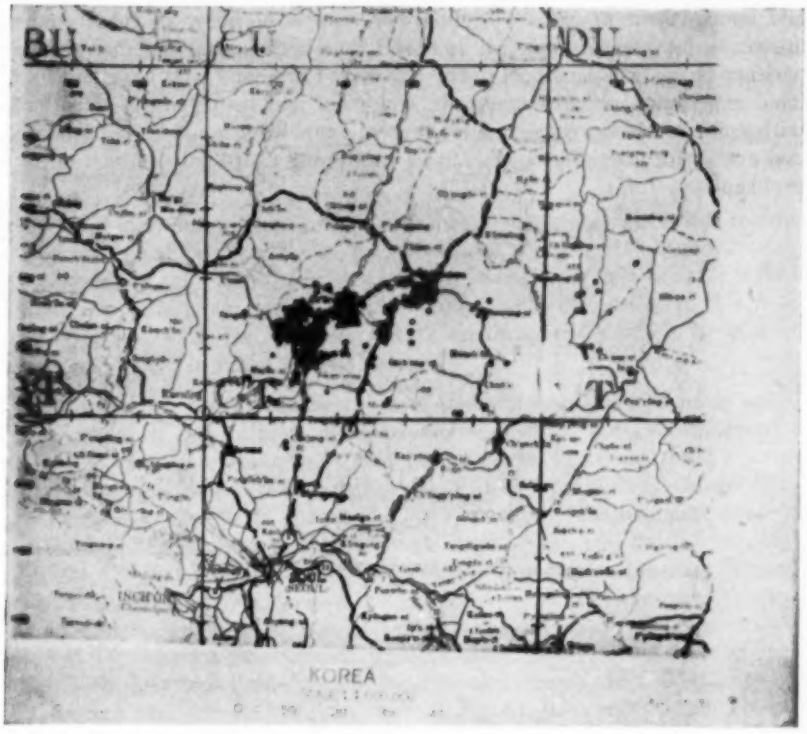



FIG. 2.

appears as if the answer to the question of when and how this disease was introduced to South Korea must await further study.

In the present epidemic there has been a steady reduction of the case fatality rate. It is not possible at the present time to determine whether this is a real or an apparent reduction. As the epidemic progressed, increased knowledge and awareness of the new entity brought to light mild cases, indicating that such cases may have been missed early in the epidemic. This increased awareness and diagnosis of mild cases may be responsible

for the apparent decrease in the case fatality rate. It is to be noted that the Japanese, on the other hand, reported that the cases observed during the fall peak were more severe than those of the spring peak.

It is expected that the passage of time will, on the one hand, permit a more complete analysis of such epidemiologic data as have been collected, and, on the other, remove security restrictions which prevent presentation of all of the data. However, many studies have been under way to define better the clinical picture, the pathology and the pathologic physiology of this disease, and to develop rational and improved therapeutic procedures and management of cases. Preliminary reports of many of these studies are ready for presentation. It is hoped that by bringing together the experience of medical personnel of the Far East Command who have had first-hand experience with the diagnosis, treatment and management of patients with epidemic hemorrhagic fever, present knowledge may be consolidated and evaluated, providing a basis for a continuing coördinated attack on this problem.

# THE EARLY FIELD DIAGNOSIS OF EPIDEMIC HEMORRHAGIC FEVER*

By William F. Ganong, 1st Lieutenant, MC, Edward Zucker, Captain, MC, Carroll K. Clawson, Captain, MC, Edward C. Voss, 1st Lieutenant, MC, Milton L. Klotzbach, 1st Lieutenant, MC, and Kenneth A. Platt, 1st Lieutenant, MC

During the summer and autumn of 1951, the 1st Cavalry Division was deployed south and west of Yonchon, the center of the area from which the vast majority of cases of epidemic hemorrhagic fever originated. Between August 1 and December 10, 1951, a large number of cases clinically diagnosed as this disease were evacuated through the clearing station of the Division. Because the early features of this disease are difficult if not impossible to differentiate from other acute infections, it was felt that a report of experience gained from these cases would be of interest in emphasizing the points most helpful in the early diagnosis of epidemic hemorrhagic fever.

There is little in the initial symptomatology that is peculiar to this disease. Certain symptoms, however, were characteristic enough to arouse suspicion. These included the following:

*1. Headache:* The headache in early hemorrhagic fever is most commonly frontal or retroörbital. It is usually severe and not particularly related to movement of the eyes. This pain and the associated mild photophobia led the patients to hold their eyes shut or to lean on their elbows with their hands over their eyes. Indeed, this eye-holding was common enough to be jokingly referred to as "hemorrhagic fever position."

*2. Back Pain:* Pain in the lumbar area is a remarkably constant finding early in the course of this disease. Generalized myalgia is also present, but it is characteristically most marked in the lumbar region. Its severity is indicated by the fact that several patients were admitted to the clearing station with their backs taped. The location and nature of the pain suggest a renal origin, but, unlike the pain in renal disease, tenderness in the costovertebral angle is not usually marked.

*3. Gastrointestinal Symptoms:* Anorexia is an almost universal and often an initial symptom. Nausea and vomiting, on the other hand, although common, are not constant early findings. The striking feature of these complaints, however, is the absence of other gastrointestinal symptoms. Abdominal pain has been mentioned as a common complaint, but our experience did not bear this out. Indeed, in our cases, pain was rare and diarrhea did not occur.

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From the Clearing Company, 15th Medical Battalion, 1st Cavalry Division.

Physical findings were usually of more diagnostic help than symptoms, even in the early stages of epidemic hemorrhagic fever. The large subconjunctival hemorrhages, considered a hall-mark of the disease, were uniformly absent, and the widespread petechial rash was rarely present in the early days of the illness. The rapidity of development of the hemorrhagic phenomena varied greatly from case to case. Certain physical findings, however, were remarkably constant, even in early cases, and characteristic enough to be of diagnostic weight. These included the following:

*1. Appearance:* The patient with hemorrhagic fever characteristically looks and acts ill. Though consciousness is clear and the patient is not irritable, the headache, nausea and myalgia make him very uncomfortable. In addition, the headache and photophobia make him squint slightly, while the suffused red face and the conjunctival changes all contribute to make him appear sick. This is in considerable contrast to patients with respiratory infections, malaria and similar common infections who, with equal degrees of fever, look well by comparison.

*2. Erythema of the Face and Neck:* One of the most typical early findings in our cases has been a diffuse reddening of the skin, most marked over the face and the V of the neck, but sometimes also seen over the chest and back. This scarlatiniform erythema is more than a simple febrile flush; it is often severe enough to resemble a severe sunburn. Close inspection of the skin often shows dilated small vessels in addition to the reddening, which blanches on pressure, the whole picture resembling in many way the facies of Cushing's syndrome.

*3. Conjunctival Injection and Edema:* Although conjunctival hemorrhages are absent in the first days of epidemic hemorrhagic fever, conjunctival changes are usually present and often characteristic enough to be of considerable aid in diagnosis. Slight edema of the upper lids gives the patient a bleary-eyed appearance. The conjunctivae, both bulbar and palpebral, show a fine and sometimes intense injection. The picture resembles that seen in measles but without lacrimation. Petechiae occasionally appear on the conjunctivae, but in our experience they were not common and did not appear early.

*4. Pharyngeal Injection:* Intense pharyngeal reddening with dilation of small blood vessels but without significant pharyngeal pain was found to be typical of this disease. Because of this pharyngeal reaction, a large number of cases were evacuated from forward units with the diagnosis of acute pharyngitis or tonsillitis. The difference between these cases and patients with more benign types of pharyngitis, however, was the absence of significant dysphagia or sore throat in the hemorrhagic fever patients.

*5. Petechiae:* Petechial hemorrhages were frequently absent in early cases. Search for petechiae was conducted in each case, however, because it was found that approximately half the early cases showed a few spots. The first place the rash appeared was usually the palate. The petechiae

were seen in small groups and usually appeared after the pharyngeal injection. Twelve to 24 hours after palatal petechiae appeared, they could also be found in small numbers along the axillary folds. From there they spread onto the lateral chest wall and neck; occasionally they were also found in the conjunctivae, but this was uncommon at division level. The importance of searching for petechiae lies, of course, in the fact that, when found, they are diagnostic.

Detailed laboratory studies are admittedly impractical in the field. However, blood counts, smears and urinalyses are easily done at Clearing Company level, and these laboratory tests were found to be of great assistance in diagnosing hemorrhagic fever. This was particularly true in the holding wards of the company, where frequently repeated laboratory determinations helped greatly to delineate the early laboratory picture of the disease. Findings of most value in field diagnosis included the following:

*1. Albuminuria:* The presence of albumin in the urine, particularly in large amounts, is a typical but not universal finding in hemorrhagic fever. Some patients even developed petechial rashes before albuminuria was detected. When albumin is present, however, it is of great diagnostic importance, since in the absence of dehydration the finding of more than a trace of albumin rules out most of the conditions from which this disease must be differentiated. It was also discovered at our holding wards that albumin may appear in the urine with great rapidity. Several cases were followed with urinalyses twice or three times a day. It was not unusual in these cases to find urinary albumin negative at one time but 4-plus only three to six hours later. It is therefore important not only to check the urine frequently but also to ignore previously negative reports if other findings suggest the diagnosis.

*2. "Mononuclear Cells" in the Urine:* A laboratory finding apparently characteristic of epidemic hemorrhagic fever is the presence of large numbers of oval bodies in the urine. These bodies are two to four times the size of a white blood cell and probably represent mononuclear phagocytes or renal tubular cells, since they show a distinct cell wall and one or sometimes two nucleus-like masses in the center. They often contain vacuoles of a refractile material resembling fat. They appear in the urine often before albumin and, in our experience, seem to be a dependable diagnostic aid.

Because this finding has not been reported elsewhere, a pilot study of its significance was attempted at the clearing station. Large numbers of these bodies were found in the urine of 35 consecutive cases of hemorrhagic fever. They were absent from 14 normal and several pathologic urines from patients with albuminuria or other urinary findings from other causes. That these "cells" may not be specific for hemorrhagic fever is suggested by the fact that a few of them were found in one presumably normal urine. Indeed, on the basis of this short and incomplete study, it is manifestly impossible to draw any detailed conclusions on the nature or the significance of these

bodies. However, their abundant occurrence in early hemorrhagic fever and their appearance in some cases as the first sign of renal involvement suggest that they may be of unique value in early diagnosis.

*3. Lipiduria:* Another incidental finding of considerable theoretic interest has been the demonstration of large amounts of a fatty substance in the urine of hemorrhagic fever patients. This material is ether-extractable and stains with fat stains. The amount present parallels the severity of the albuminuria, although removal of the albumin by heat and acetic acid precipitation leaves large amounts of the ether-extractable substance in the filtrate. The significance of this finding has not been determined. Its clinical importance, however, lies in the fact that droplets of free lipid are occasionally seen in the urine. These resemble and have been mistaken for red blood cells, although they are globular, refractile and quite distinctive upon close inspection.

*4. Polymorphonuclear Leukocytosis:* A rise in the white blood cell count, due mainly to an increase in polymorphonuclear leukocytes, is a reasonably constant finding in this disease. Because of its non-specific nature, however, its value is limited, although white blood counts and blood smears help in ruling out such diseases as influenza, malaria, infectious mononucleosis and early infectious hepatitis, diseases sometimes confusingly similar to early hemorrhagic fever.

The abovementioned symptoms, signs and laboratory findings, taken in total, allow a reasonably accurate diagnosis of epidemic hemorrhagic fever in most cases. They are of particular value, however, in diagnosing atypical cases. Approximately 5 per cent of our cases varied enough from the usual pattern to be remarkable. These cases fell roughly into three groups:

*1. Cases Without Fever:* During the period when hemorrhagic fever was most common, several patients were admitted to the clearing station with complaints of weakness, giddiness, anorexia, back pain and sometimes headache. They all had temperatures under 99° F., and in most cases were admitted to the holding wards. Subsequently, they all developed moderate albuminuria, nausea and a petechial rash, although their temperatures remained normal for the three-to-four day holding period. All were evacuated, and study in rear hospitals confirmed the diagnosis of epidemic hemorrhagic fever.

*2. Cases Presenting as Combat Exhaustion:* A few patients were evacuated to the clearing station diagnosed as combat exhaustion. These cases, possibly because of their personality make-up, complained only of vague myalgia, feeling "rotten," or "unable to take it any more." Two of them had myriad complaints, including most of the symptoms of hemorrhagic fever, but these were so overlaid with seemingly functional symptoms that they were overlooked. Fortunately, a temperature reading is taken on all psychiatric cases admitted to the clearing station, and after the first few

cases of this type were discovered because they had fever, it became routine also to do urinalyses on any psychiatric case whose story was at all suggestive of hemorrhagic fever.

*3. Fevers of Unknown Origin:* Cases presenting with fever as their only finding are rare but do occur. Two patients of this type were seen during the month of November. Both denied all symptoms except chilliness and fever, and both had negative physical examinations and laboratory studies when first seen. They subsequently developed petechiae and massive albuminuria, and one of them went into shock without showing other signs of the disease.

Differential diagnosis must, of course, include all acute febrile illnesses common in a young adult male population. Our most common diagnostic errors are illustrated by the cases admitted to the holding wards with other diagnoses who subsequently developed typical epidemic hemorrhagic fever. There were 13 such patients. Four were diagnosed influenza, four acute tonsillitis, two acute pharyngitis, and one each bronchopneumonia, chronic bronchitis and "upper respiratory infection." This experience emphasizes the confusion that may result because of the pharyngeal reaction in hemorrhagic fever.

Another point of some importance is that these patients sometimes complain of cough, usually on the basis of chronic exposure to dust or to an incidental bronchitis. In a few patients, no explanation other than hemorrhagic fever could be found for persistent cough. However, if careful attention is paid to other systemic symptoms and the laboratory findings, the correct diagnosis will not be missed.

Some cases in which nausea and vomiting were prominent symptoms were initially suspected of food poisoning. Routine urinalyses on patients with vomiting helped to avoid this error.

Another condition sometimes confused with hemorrhagic fever was infectious mononucleosis. This disease is fairly common among troops, and its symptoms, especially the backache and gastrointestinal complaints, resemble those of early hemorrhagic fever. However, the lymphadenopathy, hepatosplenomegaly and high atypical lymphocyte count readily differentiate it.

A common infection which may cause confusion in its early pre-icteric stage is infectious hepatitis. The two diseases have nausea, anorexia, fever and abdominal and back pains in common. However, the absence of pharyngeal injection, petechiae and albuminuria, and the usual development of palpable liver in hepatitis differentiate it in most cases.

Finally, the headache, back pain and fever seen in malaria have sometimes led to diagnostic errors, but this disease is differentiated by the splenomegaly, the normal leukocyte count, the positive smear and the response to chloroquine therapy.

## Summary

Experience with the large number of cases of epidemic hemorrhagic fever evacuated through the clearing station of the 1st Cavalry Division in the past four months has emphasized certain findings of considerable significance in the early diagnosis of this disease. Retroörbital pain, backache, severe anorexia, nausea and emesis in the presence of fever suggest the diagnosis. Physical findings of most value are the severe "toxicity" of the patient, an intense erythematous blush of the face and neck, conjunctival and pharyngeal injection out of proportion to any pharyngeal symptoms, and, when present, petechiae which appear first on the palate and later in the axillae. Polymorphonuclear leukocytosis is of value when present, although it is far from specific. Albuminuria is an important finding but may be absent in early cases. Peculiar mononucleated bodies have been found to occur in the urine, sometimes before the appearance of albumin, and seem to be of diagnostic value. Lipiduria is also present early. The rapidity with which urinary involvement can appear and progress emphasizes the importance of repeated urinalyses during evacuation and early hospitalization.

In our hands, the disease was most commonly confused with acute pharyngitis and influenza, although infectious mononucleosis and pre-icteric infectious hepatitis must also be differentiated from early hemorrhagic fever.

Occasional atypical cases without fever, with multiple vague symptoms, or with fever as their only symptom, lead to further difficulty in diagnosis. It should be emphasized, however, that although the early picture of this disease is almost entirely nonspecific, careful study with the above points in mind will permit a reasonably accurate diagnosis in the majority of cases.



### Acknowledgments

The authors wish to express their debt to Captain John Maloney, Mobile Unit No. 1, 1st Medical Field Laboratory, for his encouragement and assistance in the laboratory technics used to study this disease. Credit is also due to the laboratory technicians of Clearing Company, especially Sergeant Thomas Atkinson, whose careful and proficient work made laboratory diagnosis of such value in the field.

# THE EARLY DIAGNOSIS OF EPIDEMIC HEMORRHAGIC FEVER—EXPERIENCES IN THE FORWARD ECHELONS OF THE MEDICAL SERVICE *

By Edward F. Counts, Major, MC, Division Surgeon, 25th Infantry Division, and Raymond Seltser, 1st Lt, MC, Division Preventive Medicine Officer, 25th Infantry Division

At Division level it is extremely important that the diagnosis of epidemic hemorrhagic fever be suspected as early as possible, so that evacuation may be instituted to take the patient to an installation better equipped to handle the numerous problems arising in the care of such patients.

In order to evaluate criteria which may be useful in considering the diagnosis, a study was made of 50 consecutive patients evacuated from a divisional sector with the diagnosis of epidemic hemorrhagic fever. The data were submitted to the Division Surgeon's Office in the form of telegraphic reports in which were listed the complete symptomatology, physical findings, and laboratory data done on the patient during his brief stay in the Clearing Station. These cases were evacuated back through a Mobile Army Surgical Hospital and our follow-up ended there. However, confirmation of the diagnosis of epidemic hemorrhagic fever came in the form of TWX from Japan, or by direct communication with the 8th Army Surgeon's Office. In this way, it was possible to obtain confirmation of our diagnosis in 40 of the 50 patients. Thus far, no word has been obtained on the other 10 and for the purposes of study, they will be classed as "Suspected Cases." The patients reviewed were evacuated from the Division Area during the months of October and November, and were handled in the same manner as any other acute infectious disease. No special attempt was made toward a research study.

## Symptoms

Acute onset of fever, chills, headache, anorexia and nausea occurred in over 50 per cent of the patients; malaise, vomiting, and backache were present in over one-third of the cases. A wide variety of other symptoms present is listed in table 1.

Twenty-five per cent of the patients had symptoms referable to the eyes, in the form of a burning sensation; "aching" of the eyeballs, especially on motion; blurring of vision; or photophobia. Abdominal pain occurred in the right upper quadrant of four patients, and in the left lower quadrant in one other. Six complained of generalized muscle aches, and two of chest pain. Cough was present in four cases, sore throat in three, and acute

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TABLE I

Epidemic Hemorrhagic Fever

| Symptom | Confirmed Cases—40 | Suspected Cases—10 |
|---|---|---|
| Fever | 33 | 7 |
| Chills | 32 | 7 |
| Anorexia | 23 | 8 |
| Nausea | 22 | 5 |
| Headache | 23 | 8 |
| Malaise | 19 | 7 |
| Vomiting | 15 | 4 |
| Backache | 14 | 3 |
| Generalized muscle aches | 6 | 1 |
| Abdominal pain | 5 | 0 |
| Eye symptoms | | |
| Burning | 4 | 0 |
| "Aching" | 3 | 1 |
| Blurring | 2 | 1 |
| Photophobia | 1 | 0 |
| Sore throat | 3 | 0 |
| Chest pain | 2 | 0 |
| Constipation | 2 | 0 |
| Diarrhea | 1 | 0 |
| Cough | 4 | 0 |
| Coryza | 1 | 0 |
| Dizziness | 1 | 0 |
| Hematemesis | 1 | 0 |

coryza in one. Constipation was a symptom in two patients, and only one had diarrhea. One patient gave a history of hematemesis at time of admission to the Clearing Station, but he was seen first on his fourth day of symptoms. It is interesting to note that there were no symptoms of urinary tract involvement in 40 patients seen in the early stages of the disease.

## PHYSICAL FINDINGS

The most consistent finding among these patients was injection of the sclerae and conjunctivae. Twenty-three of the 40 confirmed cases and five

TABLE II

Physical Examination Findings
Epidemic Hemorrhagic Fever

| | Confirmed Cases—40 | Suspected Cases—10 |
|---|---|---|
| Conjunctival and scleral injection | 23 | 5 |
| Injected pharynx | 12 | 2 |
| Periorbital edema | 11 | 3 |
| CVA tenderness | 7 | 3 |
| Abdominal tenderness | 5 | 2 |
| "Flushed" face | 5 | 3 |
| Petechiae | | |
| Eyes | 4 | 3 |
| Chest | 3 | 0 |
| Forearm | 1 | 0 |
| Prostration | 3 | 3 |
| Râles–chest | 2 | 0 |
| Back spasm | 1 | 0 |
| Hepatomegaly | 1 | 2 |
| Splenomegaly | 1 | 0 |

TABLE III

Temperatures
Epidemic Hemorrhagic Fever

| | 40 Confirmed Cases | | 10 Suspected Cases | |
|---|---|---|---|---|
| | Maximum | Minimum | Maximum | Minimum |
| Below 98° | 2 | 6 | 0 | 1 |
| 98.1–99° | 2 | 4 | 0 | 1 |
| 99.1–100° | 1 | 3 | 1 | 0 |
| 100.1–101° | 3 | 5 | 0 | 2 |
| 101.1–102° | 3 | 3 | 0 | 2 |
| 102.1–103° | 14 | 3 | 4 | 0 |
| 103.1–104° | 9 | 0 | 3 | 0 |
| 104.1–105° | 4 | 0 | 2 | 0 |

of the 10 suspected cases showed this abnormality on physical examinations. Periorbital edema was present in 11 cases, and injection of the pharyngeal mucosa was seen in 12. Petechial hemorrhages were reported in eight of the patients, occurring in the eyes of four cases, on the chest in three, and over the forearms in one. This finding occurred in patients who were first seen at least three days after the onset of symptoms. Abdominal tenderness, particularly in the right upper quadrant was elicited in five and the liver was palpable in one case. "Flushing" or "bronzing" of the skin of the face was reported in five cases. Only three patients showed evidence of prostration during this stage of their illness. Other findings were râles in the lungs of two patients, spasm of the back muscles in one, and a palpable spleen in one case.

## TEMPERATURE READINGS

The majority of patients were febrile, with temperatures of 102° and over at the time of admission. In 13 of the cases, the temperature had returned to normal by the time they were evacuated back to the Mobile Army Surgical Hospitals. Fever, therefore, seems to appear early and also remits early in the course of the disease.

## LABORATORY DATA

White blood counts were recorded in only 29 of the 40 confirmed cases and in all of the 10 suspected cases. The majority had normal white counts

TABLE IV

Maximum White Blood Count
Epidemic Hemorrhagic Fever

| WBC/mm.$^3$×1,000 | Confirmed Cases—40 | Suspected Cases—10 |
|---|---|---|
| Under 5–5.0 | 3 | 0 |
| 5.1–10.0 | 13 | 7 |
| 10.1–12.0 | 3 | 1 |
| 12.1–15.0 | 4 | 2 |
| 15.1–20.0 | 4 | 1 |
| Over 20.1 | 2 | 0 |

and differentials. Only six of these showed any significant degree of leukocytosis. The highest counts recorded were 21,000 and 43,000, each reported in one case and in each instance occurring after at least five days of symptoms.

TABLE V

Urinalysis Results
Epidemic Hemorrhagic Fever

| | Confirmed Cases—40 | Suspected Cases—10 |
|---|---|---|
| Albuminuria | | |
| Negative | 5 | 4 |
| 1+ | 9 | 0 |
| 2+ | 9 | 2 |
| 3+ | 5 | 0 |
| 4+ | 6 | 1 |
| Microscopic | | |
| Pyuria | 7 | 3 |
| Hematuria | 5 | 4 |
| Cylindruria | 2 | 2 |
| Change from normal to abnormal during stay at Clearing Station | 10 | 2 |

The information obtained from urinalysis was more helpful. Thirty-four of the 40 confirmed cases had recorded urine examinations, with 29 of these showing abnormalities. These consisted of albuminuria in all and microscopic abnormalities in 12.

In 10 cases which showed negative admission urine, albuminuria later developed. This occurred after two days of observation in two cases and after three days in eight cases.

TABLE VI

Duration of Symptoms
Epidemic Hemorrhagic Fever

| Number of Days | Prior to Adm. to Clearing | | Prior to Adm. to MASH | |
|---|---|---|---|---|
| | Confirmed Cases | Suspected Cases | Confirmed Cases | Suspected Cases |
| 0 | 1 | 0 | — | — |
| 1 | 7 | 2 | — | — |
| 2 | 14 | 1 | 1 | 1 |
| 3 | 13 | 7 | 9 | 4 |
| 4 | 2 | 1 | 15 | 3 |
| 5 | 3 | — | 9 | 1 |
| 6 | 1 | — | 5 | 2 |
| 7 | — | — | 1 | — |

The symptoms, signs, and physical findings as described above must be interpreted in terms of the stage of the disease during which these patients were seen.

As can be seen from table 6, the majority of observations were made on patients seen during the first three days of symptoms.

TABLE VII

Number of Days Observation at Clearing Prior to Evacuation
Epidemic Hemorrhagic Fever

| | Confirmed Cases | Suspected Cases |
|---|---|---|
| Less than 1 day | 7 | 2 |
| 1 day | 16 | 6 |
| 2 days | 7 | 1 |
| 3 days | 6 | 0 |
| 4 days | 4 | 1 |

Thirty of the 40 patients with confirmed epidemic hemorrhagic fever were evacuated after being observed for two days or less (table 7). Therefore, the picture as described in the body of this paper may be interpreted as representing epidemic hemorrhagic fever as seen during the first four or five days of the disease. It is easily seen that the symptoms are non-specific during this stage. There are no diagnostic physical findings. However, of the described signs, injection of the conjunctivae, sclerae and pharynx, together with periorbital edema were the most consistent findings. The mentioned bronzing of the face, and the petechial hemorrhages described as characteristic in all descriptions of the disease are not seen in significant numbers of patients this early in the course. There is nothing particularly helpful about the temperature, except for a fairly consistent elevation even on the first and second days of symptoms. If the patient is observed beyond the fourth day of symptoms, the temperature was noted to fall even though the patient's symptoms persisted. This is one well-described feature of the disease which may be seen in the forward medical installations.

The laboratory data were most helpful because of the frequency with which albuminuria occurred. Since this is one of the simplest of laboratory procedures, and apparently undergoes change from normal to abnormal within the first few days of symptoms, we consider it a valuable diagnostic aid. In an area where this disease is known to be present, any patient with non-specific symptoms and physical findings of infection deserves at least a careful urinalysis for albumin daily until the question of epidemic hemorrhagic fever has either been confirmed or resolved. In this way, it is felt that a higher percentage of patients will be correctly diagnosed and evacuated earlier and fewer evacuated with diagnoses of "fever of unknown origin."

TABLE VIII

Disposition Diagnoses of 31 Cases of Epidemic Hemorrhagic
Fever Incorrectly Diagnosed at Division Level

| | |
|---|---|
| Fever of undetermined origin | 18 |
| Infectious hepatitis | 4 |
| Malaria | 3 |
| Nephritis | 2 |
| Infectious mononucleosis | 1 |
| Immunization reaction | 1 |
| Acute gastritis | 1 |
| Tonsillitis | 1 |

During the period in which the described 50 cases were evacuated with diagnoses of medical observation, epidemic hemorrhagic fever, an additional 31 cases of the disease occurred and were evacuated with other diagnoses. These cases are tabulated in table 8.

## Conclusion

As more is learned about therapy, early diagnosis becomes important. On the basis of the above cases, even though the series is small, it may be judged that the presence of fever, chills, periorbital edema, injected sclerae and conjunctivae, and the presence of albuminuria, and particularly if there is appearance of albumin during the first two to four days is sufficient in this region to warrant evacuation with the diagnosis of epidemic hemorrhagic fever. It should *not* be expected that actual conjunctival or scleral hemorrhages; bronzing of the face; or scattered petechial hemorrhages will be seen in the Battalion Aid Stations, Collecting Stations, and Clearing Stations. Confirmation of the diagnosis will depend on following the clinical course of the disease.

# GROSS ANATOMIC FEATURES FOUND IN 27 AUTOPSIES OF EPIDEMIC HEMORRHAGIC FEVER *

By William H. Kessler, Captain, MC, *Camp Rucker, Alabama*

Since July, 1951, 40 cases whose deaths are now ascribed to epidemic hemorrhagic fever have been autopsied at the 121st Evacuation Hospital. The author has performed only 27 of these gross autopsies, and this report will be confined to this latter figure. The remaining autopsies were performed by Capt. Eugene J. Kulinski and 1st Lt. William T. Paine. These deaths occurred for the most part in cases under treatment at this hospital, though three were brought back from forward areas for autopsy because the circumstances surrounding their deaths were unknown at the time of autopsy. These three cases had not received medical care prior to their deaths, though in retrospect it was learned that each had been ill for four or five days before death. All deaths in this series occurred between the fourth and twelfth days of the disease.



Fig. 1.

The prominent features in each case (figure 1) varied somewhat according to the clinical stage in which death occurred. Three anatomic areas, however, demonstrated pathologic changes in each case. These are: (1) anterior pituitary; (2) the kidneys, and (3) the wall of the right atrium.

For the sake of convenience the gross changes will be described under systems.

*General Features:* There is usually a dusky cyanotic hue to the face, neck and upper anterior chest, which is frequently associated with multiple cutaneous petechiae. The petechiae are most noticeable in the earlier cases, whereas after the sixth or seventh day the more prominent changes may be

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ecchymoses. These ecchymoses are usually around injection sites, though they may be located at any point subjected to trauma. The extravasated blood is usually found in the subcutaneous adipose tissue or in the deeper fascial planes.

The bulbar conjunctiva presents edema, petechiae or ecchymoses, depending on the stage in which death occurred. The earlier cases—that is, those coming to autopsy on the fourth or fifth days of the disease—present edema which has been found to be directly proportional to the edema found in the retroperitoneal tissues. Petechiae and, later, ecchymoses appear. This is paralleled by similar hemorrhagic manifestations in the palate and posterior pharyngeal wall. The ecchymoses may be single, multiple or confluent, and they may entirely surround the cornea. Quite often there is evidence of nasal or oral hemorrhage or both, but this is usually found in cases after the sixth or seventh day.

After making the primary trunk incision, one frequently finds excessive fluid and scattered ecchymoses in the musculature of the thoracic and abdominal walls, and excessive quantities of free fluid appear in the peritoneal and pleural cavities.

One of the most striking features in this series has been the presence of extensive edema in the loose areolar tissues of the retroperitoneal areas. This has been consistently present in all cases dying in the fourth or fifth days of the illness and corresponds to the clinical stage of defervescence of fever and the "shocklike" state. This edema has been found to be quite extensive and involves not only the retroperitoneal tissues but also the omentum, mediastinal tissues and, as noted previously, the conjunctivae. It is apparently a diffuse reaction involving all loose areolar tissues. The tissues become very distended with clear straw colored fluid and assume a gelatinous appearance. This fluid loss, plus the fluid found in the peritoneal and pleural cavities, may account in part for the circulatory insufficiency and "shocklike" state seen clinically. This, plus the vascular dilation, could certainly explain a discrepancy between the circulating blood volume and the vascular bed. Whereas it is apparently true that intravenous fluids aggravate or increase the amount of such edema seen at autopsy, it must be pointed out that all three cases without antecedent medical care presented this same finding, indicating that these cases died in the "shock" phase of the disease. This edema is found even as late as the ninth day of the disease, though by comparison one gains the impression that this edema is absorbed in the stages following "shock." The absorption of this fluid, in view of oliguria, has been used in one case to explain the onset of clinical pulmonary edema approximately 48 hours after the last intravenous fluids had been given. It was noted clinically in one other case, in which venous pressures were studied, that a rising venous pressure ceased to rise following a wet phlebotomy on the eighth day of the disease. The most massive example of this edema was found in one case who died after approximately 36 hours of clinical "shock" and who had received over 6,000 c.c. of plasma as a

therapeutic measure. The degree of abdominal pain suffered by these patients is directly proportional to the degree of edema seen at autopsy.

The theory has been advanced that the basic pathologic process is a vascular paralysis leading to capillary dilatation, stasis and local anoxia, resulting in increased capillary permeability. This, in turn, produces a transudation of plasma, leading to edema, and resulting in circulatory inadequacy.

*Heart:* The heart weighs between 300 and 600 gm. It is usually firm and not dilated, though an occasional case has shown dilatation of the right atrium and auricular appendage. One consistently finds ecchymoses in the anterior wall of the right atrium. These ecchymoses may be small and scattered or confluent and involve almost the entire anterior wall. Petechiae over the ventricular epicardium are also found. The myocardium and endocardium usually show nothing of importance grossly.

*Lungs:* The weight of the lungs has varied from 300 to 1,200 gm. each. The gross findings have been congestion, interstitial edema and intrapulmonary hemorrhage. Congestion is a consistent finding, though the degree is variable. Intraalveolar edema is not so often found, and it is usually associated with the later stages of oliguria and the administration of intravenous fluids. Intrapulmonary hemorrhage has been found in only relatively few cases, and it is associated with clinical hemoptysis. The hemorrhages may be quite large, involving a segment of a lobe, or only 1 or 2 cm. in diameter. They may be single or multiple, and no particular distribution pattern has been noted. The bronchial mucosa may frequently be hyperemic.

*Liver:* Weighs 1,600 to 2,100 gm. No consistent gross anatomic features have been noted, though small subcapsular hemorrhages have been seen.

*Spleen:* The weight is between 200 and 600 gm. It frequently presents congestion of the red pulp, but often it is essentially normal. One case, not autopsied by the author, had a ruptured spleen resulting in a massive intraperitoneal hemorrhage.

*Gastrointestinal Tract:* Hyperemia and mucosal hemorrhages in the stomach are rather frequent. The relationship of this to the production of vomiting per se is not clear, but it can lead to hematemesis and melena. The intestinal tract, in addition, may show submucosal edema and thickening of the wall and congestion of the serosal vessels. Quite often one sees congestions of the free edges of the villi.

*Endocrine Glands:* The most consistent gross feature found in the endocrine glands is vascular changes in the anterior pituitary and infundibular stalk. These may appear merely as congestion, but more often there appears to be frank extravasation of blood into the substance of the gland, causing the diaphragm over the sella turcica to bulge. The pituitary may be soft, friable and necrotic. The posterior pituitary rarely shows any changes.

The adrenals in two cases have revealed gross hemorrhage. In both

cases the hemorrhage was bilateral, but in neither case was it large or extensive. The pancreas, thyroid and testes have not shown any specific gross changes.

*Kidneys:* The kidneys present classic gross changes. They are almost always large, weighing from 200 to 400 gm. each. The cut surface presents a sharp contrast between the pyramids and the cortex, and the cut surface usually bulges gently. The cortex is pale and presents a few fine petechiae. The pyramids, on the other hand, are dark red and hemorrhagic and stand out clearly. The central areas of the pyramids present necrosis. This type of picture has been seen in all cases studied. The pelves present multiple submucosal petechiae or ecchymoses. In only three cases have the hemorrhages been detected beyond the ureteropelvic junction, but the hemorrhagic phenomenon has been seen in the pelves in each case.

The bladder and prostate have not shown any remarkable gross changes.

*Brain:* The brains usually weigh between 1,350 and 1,550 gm. each. No specific gross changes have been noted in any case that may account for the disturbances of the central nervous system frequently seen in these patients.

## Summary

1. A review is presented of gross anatomic features found in 27 autopsies of epidemic hemorrhagic fever.

2. Vascular changes consisting of edema, congestion and hemorrhage are the most prominent and may be found in any organ, though the hemorrhagic phenomena are most conspicuous in the anterior pituitary, the kidneys and the right atrium.

3. Attention is called to the extensive retroperitoneal edema found in all cases autopsied in the earlier stages of this disease.

# PATHOLOGY OF EPIDEMIC HEMORRHAGIC FEVER *

By R. L. Hullinghorst, Lt. Colonel, MC, U. S. A., and Arthur Steer, Lt. Colonel, MC, U. S. A.

From the standpoint of Western medicine there has been little or no experience with epidemic hemorrhagic fever.[1] Since the early 1930's there has been a continually developing awareness by Russian workers [2] of the existence of a nosologic entity characterized by fever, hemorrhage and severe renal involvement. The disease was epidemic in nature, characterized by an initial outbreak in spring or early summer, relative quiescence during August, and a second wave of more marked incidence in September, October and November. These workers have established reasonably well its non-bacterial origin and have reported failure to isolate a viral agent despite use of many varieties of laboratory animals. A group of Japanese workers [3, 4, 5, 6, 7, 8, 9, 10, 11] confirmed many of these facts in the study of an identical disease occurring in sharply defined areas of Manchuria during the period 1939–1945. This latter group claimed to have isolated a filterable agent capable of reproducing the disease on transmission in selected animal species. Based on such experimentation, they postulated that the disease was caused by a virus existing in a field rodent (*Apodemus agrarius*) and was transmitted to man by the mite *Laelaps jettmari* (Vitzhum). The sudden termination of World War II interrupted further activities by this group, with many factors yet unknown and some basic work not confirmed by repetition. The transmissible agent was lost at the time of surrender or shortly thereafter.[12]

Although observers in this laboratory and others anticipated the possible appearance of this disease in UN Forces in Korea,[13] no cases of the disease were identified in such troops throughout 1950. Review of autopsies performed on such troops further supports the absence of the disease in 1950. The disease did appear in the usual pattern in 1951. Clinical and epidemiologic features are being currently reported by others. It is the purpose of this paper to describe the pathologic lesions in fatal cases of this disease.

## Material and Methods

Most of the fatalities occurred in Korea, and autopsies were performed by medical officers available at the particular field installation. Tissues and protocols were then submitted to this laboratory for further examination. Because of the military medical situation, especially in the more active medical units, the autopsy material and protocols were sometimes incomplete.

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Other patients died in Japan, and autopsies were performed by pathologists at larger hospitals or by members of this organization. Although such examinations were more thorough, the clinical record of the first few days was often incomplete as the onset of disease usually occurred in forward units in Korea. The clinicopathologic correlations presented herein are therefore based on somewhat incomplete data. The lack of weights of organs and of representative sections in some of the cases is explained on these grounds.

All tissues were fixed in 10 per cent formalin, and routine sections were stained with hematoxylin and eosin. In addition the following special stains were used as indicated: Giemsa, Brown and Brenn modification of the gram stain, MacCallum-Goodpasture modification of the gram stain, Kinyoun acid-fast stain, Warthin-Starry, Levaditi, Wilder reticulum stain, Weigert's elastic tissue stain, Masson trichrome stain, phosphotungstic acid hematoxylin, melanin, fat, Dominici toluidine blue stain, Gomori's iron stain, and Mayer's amyloid stain. No microörganisms could be demonstrated in other than secondary processes, such as complicating bronchopneumonia. No structures resembling rickettsiae or specific inclusion bodies were found.

Through the early phase of the epidemic (June and July), most cases were diagnosed as leptospirosis. The complete absence of icteric cases, the negative results of intensive efforts at isolation of leptospira from clinical and autopsy material, and the lack of significant agglutination titers in acute and convalescent sera against strains of leptospira common to this area refuted this diagnosis. Finally, a representative group of paired sera showed an inability to agglutinate in significant dilutions any of a broad spectrum of 12 strains of leptospira.

Intensive attempts to confirm the viral etiology by isolation of a viral or rickettsial agent have been carried out and are continuing. Material used has been whole blood, serum, plasma, blood clot, marrow, urine, pharyngeal washings, and tissue suspensions of kidney, liver, spleen and lymph node. Such specimens have included many inoculated immediately after collection, as well as those transported or stored at zero and minus 70° C. Standard accepted methods for isolation of virus or rickettsia were applied without success. Other more unusual approaches and animal hosts have been used, in addition to some recommended by the original Japanese investigators.[14] To date the following animals have been used: white mice (suckling and weaned), hamsters (immature and mature), guinea pigs (immature and mature), rabbits, monkeys, kittens, horse, and embryonated eggs. Routes of administration have varied with inoculum and animal, have been used alone and in combination, and have included: intracutaneous, subcutaneous, intramuscular, intraperitoneal, intracerebral, yolk, amniotic and allantoic, corneal scarification, intratesticular and intravenous. Serial blind passage has been performed in a representative group in an attempt to encourage adaptation. Results have been negative up to the time of preparation of this report.

## Criteria for Diagnosis

Because no specific diagnostic test was available, all autopsy material received at this laboratory during the Korean War was reviewed. Fifty-seven patients who died during the period April 1, 1951, through December 1, 1951, had suggestive clinical findings and consistent morphologic changes of epidemic hemorrhagic fever. In addition, four cases showed typical morphologic changes without clinical recognition. These included one suicide and three patients dead on arrival at a hospital. Six cases diagnosed clinically as possible epidemic hemorrhagic fever were excluded when autopsy demonstrated another cause of death and none of the typical findings of epidemic hemorrhagic fever. Death in these excluded cases was due to peritonitis, hemolytic anemia, cirrhosis of the liver, meningococcus septicemia, acute poliomyelitis and methyl alcohol poisoning. The majority of the accepted cases fell into a definite, recognizable pattern, although a few were in a group in which the pathologic findings showed slight variations. The latter were cases of either very short or prolonged duration and were considered valuable as showing early or late changes. A total of 61 cases form the basis of this report.

## Clinical Course

The typical clinical course is being described by others. In the fatal cases, oliguria, anuria, uremia, one or more episodes of shock, and occasionally severe hemorrhage and pulmonary edema were prominent in the terminal clinical picture. During the first few days there was a leukopenia, sometimes accompanied by a mild transitory thrombocytopenia. This usually was followed by a leukemoid reaction, with total white blood cells as high as 93,000/mm.[3]

## Pathology

The pathologic lesions of epidemic hemorrhagic fever have been described by Tokoro,[11] Honzin et al.[4] and Leibin.[15] Seven cases lent by Tokoro and three cases lent by Kasahara were reviewed, and we are convinced that the pathologic changes are identical in the fatalities in Manchuria in 1939–1945 and in UN troops in Korea in 1951.

Three distinct and sometimes separate processes were regularly encountered. The most striking was a peculiar necrosis seen in decreasing order of frequency in the kidney, pituitary, adrenal and, rarely, in the pancreas and liver. The necrosis was of a bland, coagulative type suggesting infarction, although occlusion of related vessels was never demonstrated. These areas varied in size from microscopic to more than 1 cm. in diameter. They were frequently but not always surrounded by hyperemic tissue and hemorrhage.

Less striking but much more frequent was the alteration in the vascular system. There appeared to be widespread capillary damage, manifested by dilation, engorgement, diapedesis of red blood cells, and capillary rupture.

Peculiarly, the extravasated blood cells remained well preserved, exciting little or no inflammatory reaction and showing little tendency to disintegrate. Although endothelial cells sometimes appeared swollen, this was neither a marked nor a constant feature, and no consistent impression or suggestion of endothelial reaction, such as proliferation, could be gained. Likewise, thrombi were rarely encountered. The few seen on exhaustive search were no more frequent than could be found with equally intensive search of any autopsy material. In only two cases was a definite arteriolitis present. In such instances the inflammatory reaction closely resembled that of a florid polyarteritis.

The third general feature of note was a cellular infiltrate consisting mainly of mononuclear cells. The majority of these cells resembled tissue macrophages. A second type of large mononuclear cell present was identical with cells commonly found in vascular channels, particularly in sinusoids of the liver and spleen. These were believed to be immature leukocytes.

TABLE I

Weights of Organs

| Organs | No. of Cases | Weights of Organs in Grams | |
|---|---|---|---|
| | | Average | Extremes |
| Kidneys* | 46 | 521 | 300–900 |
| Heart | 46 | 357 | 200–500 |
| Spleen | 46 | 243 | 120–600 |
| Liver | 45 | 1868 | 1200–2650 |
| Lungs* | 41 | 1270 | 225–2340 |
| Brain | 39 | 1418 | 1250–1700 |

* Paired organs are recorded as total combined weight.

Plasma cells and lymphocytes were readily recognized, and in some instances neutrophils, eosinophils and mast cells were seen. An unusual aspect was the frequent lack of relationship between such foci of cellular infiltration and those of necrosis and hemorrhage.

*Genitourinary System:* The kidneys were so prominently, consistently and dramatically involved it is probable that a diagnosis would be open to question if some degree of change were not found. They were almost always increased in weight, the single exception being in the patient who lived 29 days after onset of his disease. The combined weight of both kidneys varied from 300 to 900 gm. and averaged 521 gm. (table 1). Unilateral or bilateral perirenal hemorrhage was frequent. The renal capsule was easily stripped from a smooth, sometimes slightly injected surface. On section there was bulging of the cortex, which appeared pale on comparison with the medulla (figure 1). The medulla was always markedly congested and very frequently hemorrhagic. The corticomedullary junction was thus made very distinct. In the center of the pyramids in some cases there were poorly demarcated, pale, soft areas of necrosis which were surrounded on all sides by red, congested and hemorrhagic medullary tissue. Except for diffuse and generally intense submucosal hemorrhage, the pelvis showed no changes.

Frequently there were submucosal petechiae in the urinary bladder. The prostate, seminal vesicles and testicles generally showed no gross changes.

Microscopically, glomeruli in some cases appeared congested, whereas in other instances engorged glomeruli were limited to the juxtamedullary zone. In the cases of longer duration, glomeruli sometimes showed increased cellularity of a slight degree, apparently due to endothelial proliferation. Albuminous precipitates were frequent in the glomerular space and in the dilated proximal and distal convoluted tubules in the cortex. Usually




FIG. 1. Kidney of epidemic hemorrhagic fever. The cortex is sharply demarcated from the congested and hemorrhagic medulla. The papillae contain pale areas of necrosis. There is submucosal and peripelvic hemorrhage.

vessels were not prominent in the cortex, and cellular infiltrates were not seen. At the corticomedullary junction there was marked congestion extending into the pyramids (figure 2). Tubules of the loops of Henle and collecting tubules were surrounded by dilated, engorged vascular spaces and extravasated blood (figure 3). The tubules frequently showed degeneration of the epithelium. Foci of epithelial regeneration sometimes contained many mitotic figures. Casts of all types, including pigmented casts, were present. In some cases the pyramids contained small foci of bland ischemic necrosis resembling infarcts; in others, these extended toward the renal papilla as bands of necrosis lying between congested vessels and streaks of hemorrhage, and in the most severe instances the entire center of the pyramid and renal papilla was necrotic (figures 4 and 5). At first appearance the severe

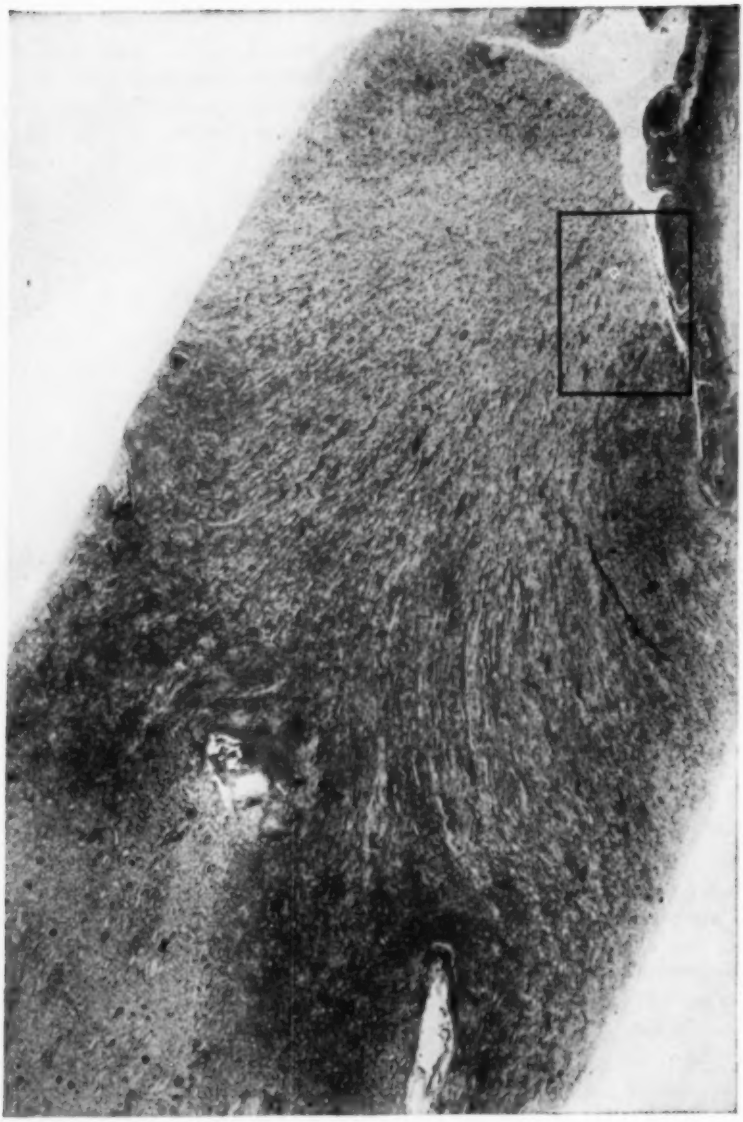


FIG. 2. Kidney of epidemic hemorrhagic fever. Hemorrhage is marked at corticomedullary junction and beneath mucosa of pelvis.



FIG. 3. Higher magnification of area indicated in figure 2. Focal hemorrhages in renal medulla. Tubules contain casts and desquamated epithelium.

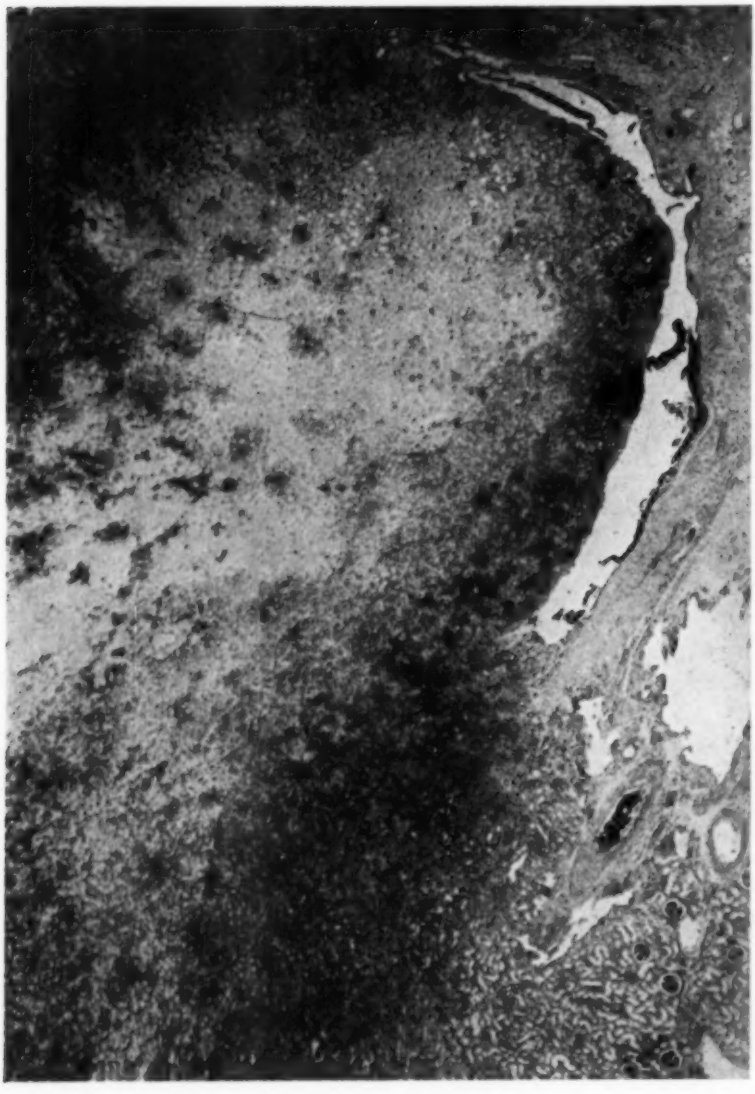


FIG. 4. Kidney of epidemic hemorrhagic fever. Central necrosis of pyramid with congestion and hemorrhage in subcortical zone.

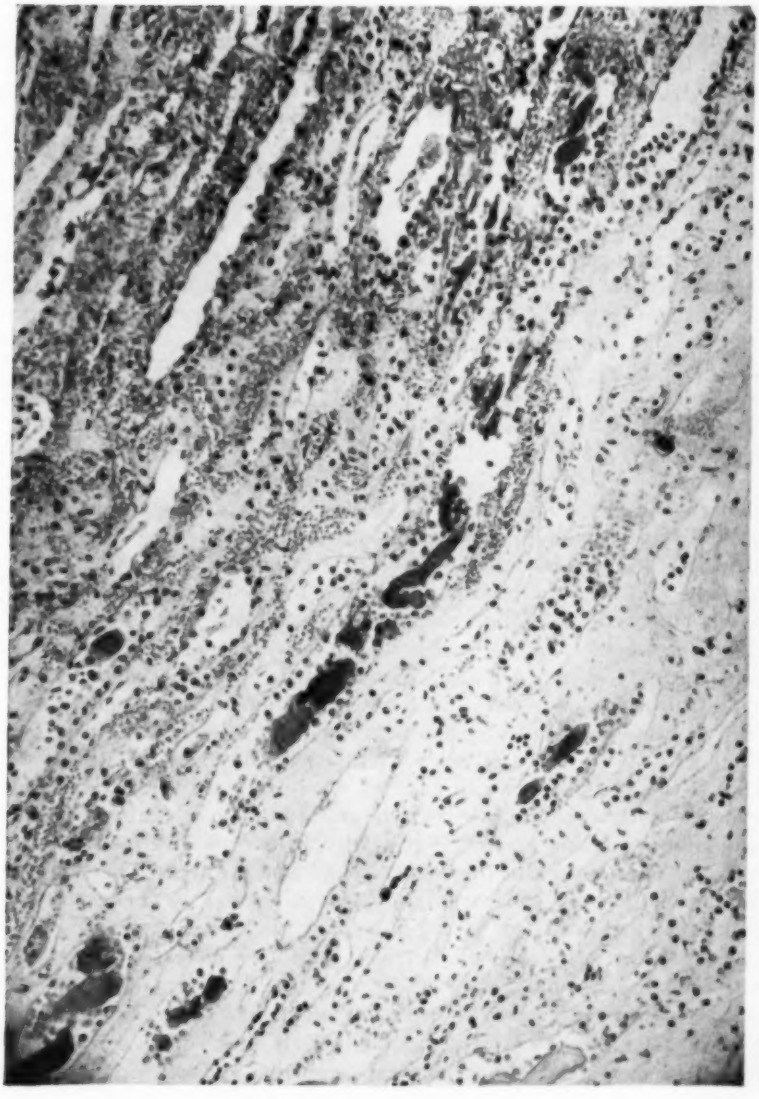


FIG. 5. Kidney of epidemic hemorrhagic fever. Higher magnification showing necrosis, casts, congestion and hemorrhage in medulla.

necrosis suggested necrotizing papillitis, but it was not typical in location, was usually more extensive, and lacked inflammatory reaction. Some degree of congestion and hemorrhage was present in all cases examined, while only 67 per cent of the cases showed evidence of medullary necrosis.

The epithelium over the papillae was frequently lacking, even though the opposing pelvic epithelium was intact. There was some suggestion that this was not entirely an artifact, in that, where the former persisted, the cytoplasm of these cells contained numerous homogeneous, sharply defined, salmon-colored globular masses which varied considerably in size. Similar "hyaline" droplets could be found in the epithelium of the larger collecting tubules but not in the epithelium of pelvis or ureter. Submucosal pelvic hemorrhage was frequently present, usually associated with a moderate inflammatory reaction. Sometimes the walls of vessels in such areas showed fibrinoid changes or cellular infiltration. However, this was believed to be secondary to the inflammation present in the area rather than a primary cause.

The testicle showed interstitial perivascular foci of mononuclear cell infiltration in some cases. Some cases had focal hemorrhages in the prostate. Submucosal petechiae of the urinary bladder showed no inflammatory or other reaction.

*Endocrine Glands:* In almost all cases, the pituitary was soft and hemorrhagic. Microscopically, in 31 of 40 autopsies the anterior lobe showed the typical foci of necrosis resembling infarcts. In 13 cases almost the entire anterior lobe had been destroyed, with only a few cells persisting beneath the capsule (figure 6). In almost all of these the necrosis extended into the infundibulum, where it was associated with hemorrhage. The posterior lobe and the pars intermedia also contained foci of hemorrhage but no necrosis. In the few cases in which the hypothalamus was examined there were foci of hemorrhage in the mammillary bodies and at the origin of the infundibulum. No evidence of vascular occlusion was found.

In 27 of the 59 cases in which adrenals were examined there were focal hemorrhages, usually in the fascicular layer. In 11 cases, large areas of coagulation necrosis were present (figure 7). In one case the medulla was also necrotic. In no case was there an entire adrenal involved.

The thyroid, thymus and parathyroid glands showed no changes other than congestion and occasional focal hemorrhage.

*Cardiovascular System:* The heart was sometimes increased in weight, the extremes being 200 and 500 gm. and the average 357 gm. (table 1). In 11 of these cases, the heart weighed more than 400 gm. Subepicardial petechial hemorrhages were frequent. Generally the right atrium was dilated and prominent because of marked hemorrhagic discoloration. The other chambers showed no gross changes, although in some there were marked subendocardial hemorrhages. No valvular or appreciable coronary changes were evident.



FIG. 6. Pituitary gland showing hemorrhage and necrosis of almost the entire anterior lobe. The infundibulum and adjacent portion of posterior lobe contain small focal hemorrhages.

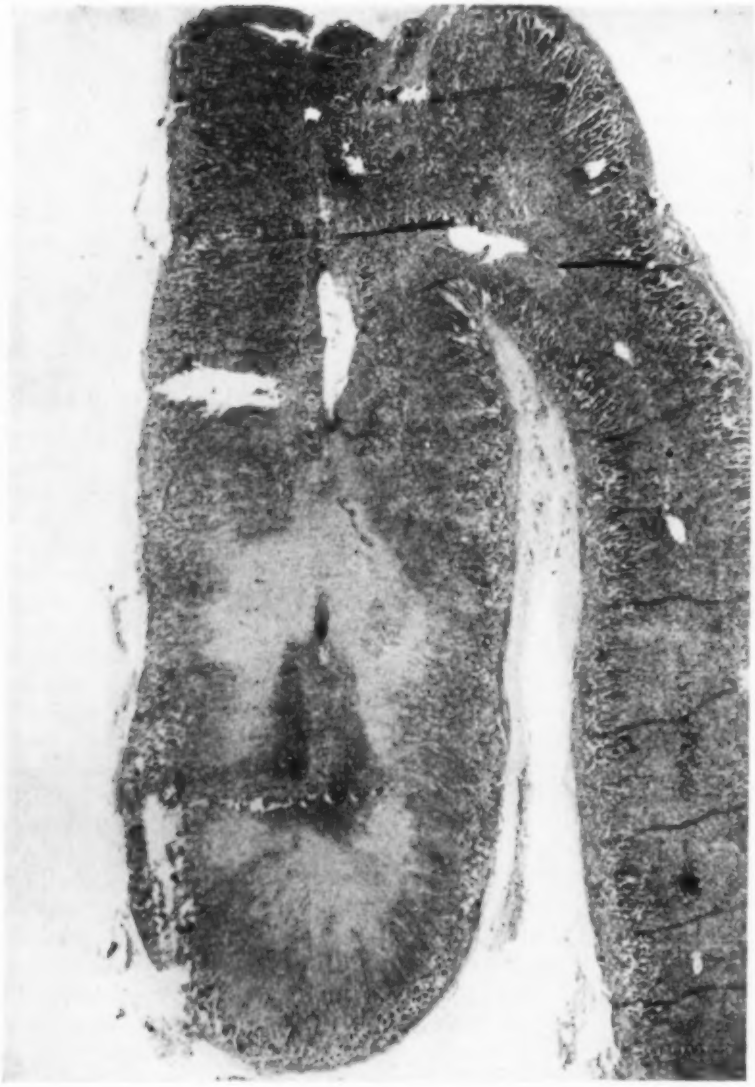


FIG. 7. Adrenal showing an extensive area of necrosis.

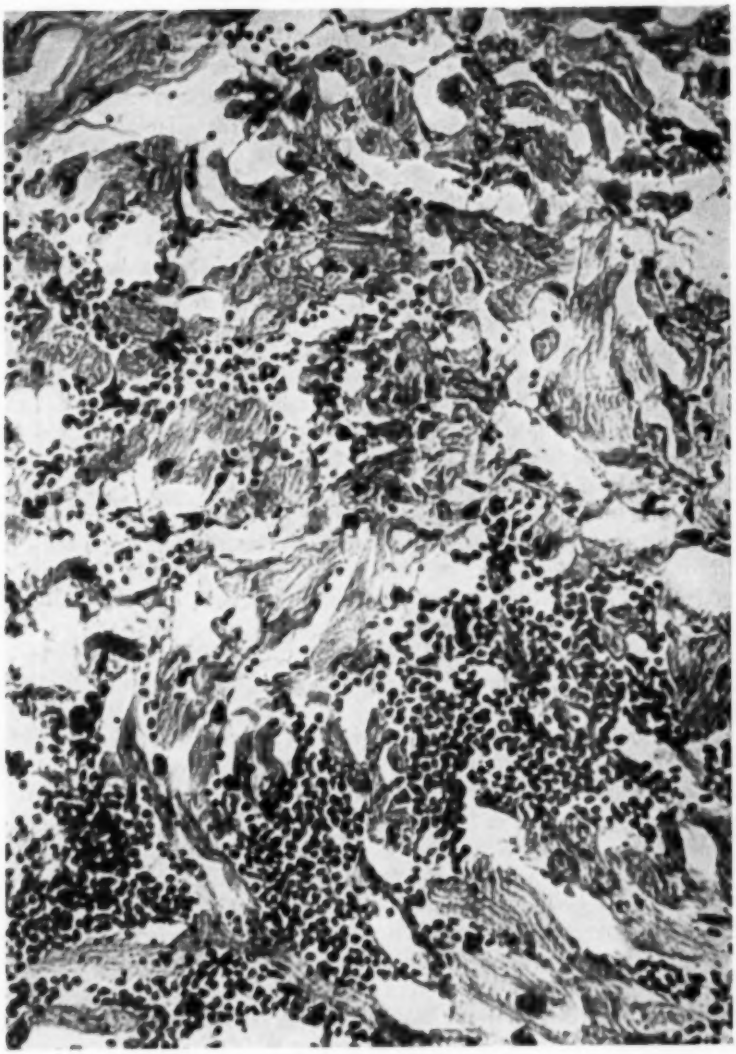


FIG. 8. Right atrium. There are diffuse hemorrhage and interstitial edema.

Microscopically, sections of the right atrium almost always showed marked diffuse hemorrhage (figure 8). Often this was not associated with an inflammatory reaction but was accompanied by interstitial edema. The left atrium showed hemorrhage less frequently than the right. However, the typical diffuse interstitial infiltration of mononuclear cells was much more frequent in the left atrium (figure 9). This infiltrate involved adjacent portions of the ventricles (figure 10) but appeared to be less prominent toward the apex. The endocardium frequently showed a diffuse, mild infiltrate of similar cells, so that the endothelium appeared three or four layers thick. This was not recognizable on gross examination. Similar inflammatory cells were present in the epicardium. Anitschkow myocytes and mast cells were also present. The areas of subendocardial hemorrhage showed no reaction. Large vessels generally showed no changes except for mild perivascular reaction about the adventitial vessels extending into the media of the aorta. In two cases the intima of the aorta contained a mild diffuse mononuclear cell infiltration.

*Hematopoietic System:* The spleen was increased in weight, averaging 243 gm., with extremes of 120 and 600 gm. (table 1). On section, follicles were less prominent than usual, and there was diffuse congestion. No distinct hemorrhages or infarcts were seen. In one instance there was a spontaneous rupture of the spleen.

Microscopically, the spleen was consistently engorged. Germinal centers were not apparent, and follicles were small. Frequently, large cells resembling megakaryocytes were seen, and in a few cases foci of extramedullary myelopoiesis were present. In addition, the sinusoids contained a large variety of cells, including many large mononuclear cells, plasma cells, polymorphonuclear leukocytes and eosinophils. Trabeculae and vessels of the spleen showed no significant changes except for diffuse intimal accumulation of mononuclear cells.

Lymph nodes were somewhat enlarged and edematous. The sinusoids contained cells similar to those found in the spleen. Here, too, active germinal centers were characteristically absent.

Bone marrow smears and preparations showed considerable variation from case to case. Generally there was increased cellular proliferation, including a small number of plasma cells, but no specific changes were recognizable. No intracellular inclusions or rickettsiae were found. In the fatal cases the highest recorded levels in peripheral blood counts were: white blood cell count, 93,000; red blood cell count, 9,980,000; hemoglobin, 21.7 gm. per cent, and hematocrit, 70 per cent. In a few cases during the febrile period it was recorded that no platelets could be found on smears, and platelet counts in other instances were as low as 40,000/mm.[3]

*Liver:* Although the liver was frequently increased in weight, there was little evident change grossly. The average weight was 1,868 gm., with extremes of 1,200 and 2,650 gm. (table 1). The gallbladder and extrahepatic ducts showed no changes. Microscopically, a few cases showed focal

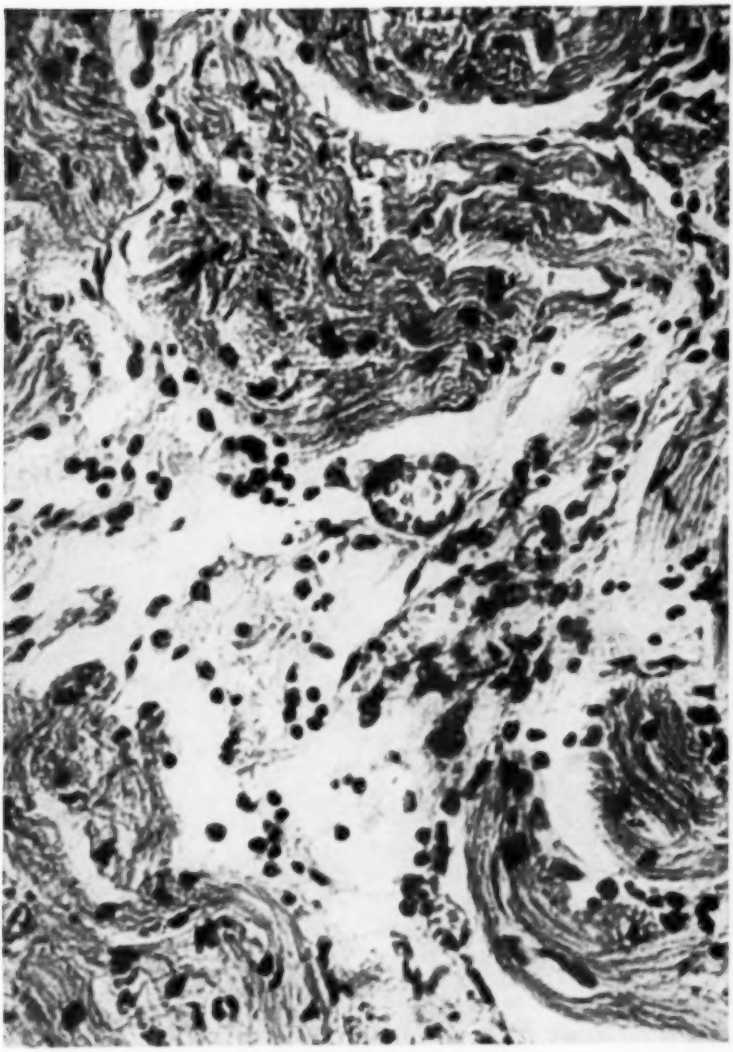


FIG. 9. Left atrium. There is diffuse mononuclear cell infiltration. The small vessel shows a suggestion of endothelial proliferation.



FIG. 10. Left ventricle—focal infiltration of mononuclear cells.

midzonal necrosis, but in only two cases was this at all prominent. In most cases the sinusoids contained numerous nucleated cells, but in only two cases was there definite evidence of extramedullary myelopoiesis. Periportal infiltrates were frequent and consisted of mononuclear cells and eosinophils. There was no evidence of bile duct obstruction, inflammation or proliferation.

*Pancreas:* In some cases the pancreas was described as being firmer than normal. In 18 of 47 cases there was a definite mild to moderate, diffuse interstitial infiltration of mononuclear cells (figure 11). These were some-

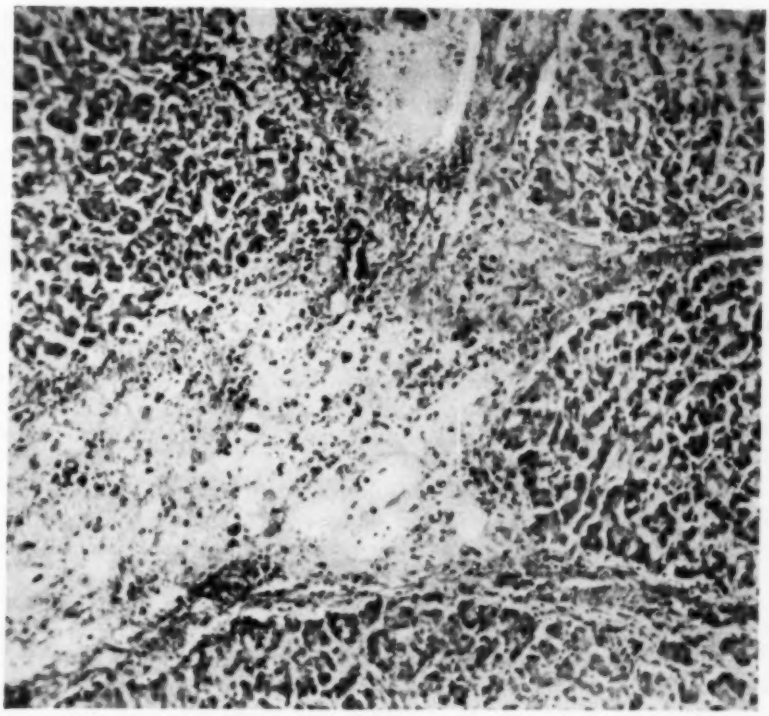


FIG. 11. Pancreas—diffuse interstitial infiltration of mononuclear cells with edema.

times associated with interstitial hemorrhage. In some cases there was marked congestion of some of the islands of Langerhans. In three cases there was necrosis limited to a few individual islands of Langerhans and sometimes surrounding acini.

*Gastrointestinal Tract:* The gastrointestinal tract frequently showed intense mucosal congestion, submucosal hemorrhage and fresh and old blood in the lumen. Sometimes the entire gastric mucosa was hemorrhagic.

Microscopically, a mild superficial esophagitis was frequently seen. Oc-

casionally this was severe and even associated with ulceration. In such cases the epithelium showed evidence of regeneration. Many cases showed a diffuse, superficial gastroenteritis, frequently associated with marked mucosal and submucosal congestion and hemorrhage. The small intestine frequently showed submucosal edema. Lymphoid follicles in the mucosa were generally small and showed no evidence of unusual activity.

*Skin:* In 24 cases in which the skin was examined, little change was noted in the epithelium other than an undue amount of melanin pigment. The vessels in the subpapillary layer of the corium were consistently prominent and dilated, and showed a mild perivascular mononuclear cell infiltrate. Mast cells were unusually frequent and prominent in this infiltrate. Hemorrhages were seen in the corium and subcutaneous tissue. Their size and distribution suggested a capillary origin. Abnormality of larger vessels could not be found.

*Body Cavities:* Fluid was frequently present, but this varied considerably in amount and location. Thirty-three of 46 patients had increased pericardial fluid varying from 30 to 150 c.c., and averaging 50 c.c. Twenty-four of 52 patients had some pleural effusion, the total amount for both sides varying from 100 to 3,000 c.c. and averaging 500 c.c. Twenty-one of 50 patients had ascites varying from 100 to 2,000 c.c. and averaging 438 c.c. In the cases of short duration there frequently was marked retroperitoneal edema, with complete obliteration of the paravertebral gutter.

*Respiratory System:* The lungs were increased in weight, averaging 1,270 gm. together, with extremes of 225 and 2,340 gm. (table 1). On section, they were congested and in some cases showed areas of pneumonia. Trachea and bronchi showed no changes.

Microscopically, the lungs showed no consistent changes. Edema, intra-alveolar hemorrhage and small foci of bronchopneumonia were seen. In two cases small typical infarcts were present. Superficial tracheitis and bronchitis were found frequently. The pleura showed no changes.

*Central Nervous System:* The average weight of the brain was 1,418 gm., with extremes of 1,250 and 1,700 gm. (table 1). There were gross foci of hemorrhage in two cases, petechial hemorrhages in 15 cases and a subdural hematoma in one case of 54 in which the brain was examined. Microscopically, there was no evidence of encephalitis, focal necrosis or specific change in the brain. The meninges were often congested. The spinal cord appeared normal. No reaction was noted in the choroid plexus. Sections of retina, peripheral nerves and ganglia showed no changes.

## Discussion

Certain of the following clinicopathologic correlations are based mainly on the disease as it was observed in fatal cases. It is evident that caution must be exercised in using such correlations to explain findings in the patients who do not succumb to the disease. As can be seen in table 2, epi-

TABLE II

Duration of Disease in 61 Fatal Cases of Epidemic Hemorrhagic Fever

| Duration of Disease in Days | No. of Cases | Accumulative Per Cent of Deaths of Known Duration |
|---|---|---|
| 2 | 1 | 1.7 |
| 3 | 1 | 3.4 |
| 4 | 1 | 5.1 |
| 5 | 5 | 13.8 |
| 6 | 6 | 24.1 |
| 7 | 9 | 39.6 |
| 8 | 10 | 56.9 |
| 9 | 3 | 67.1 |
| 10 | 6 | 72.4 |
| 11 | 4 | 79.3 |
| 12 | 1 | 81.0 |
| 13 | 2 | 84.5 |
| 14 | 2 | 87.9 |
| 16 | 2 | 91.4 |
| 17 | 1 | 93.1 |
| 21 | 1 | 94.8 |
| 26 | 1 | 96.5 |
| 29 | 2 | 100.0 |
| Unknown | 3 | |

demic hemorrhagic fever in fatal cases generally resulted in death after a relatively short course. Fifty-seven per cent died in eight days or less, and 88 per cent within two weeks of onset. This relationship is graphically represented in figure 12.

Shock and renal failure were especially prominent both during the course of the disease and as immediate causes of death. Of 57 cases with available history, 37 (65 per cent) had records of at least one episode of a shocklike state during the course of their disease, 38 (67 per cent) had oliguria or anuria, and 33 (57 per cent) had clinical uremia (table 3). The immediate cause of death in these 61 cases of epidemic hemorrhagic fever is given in table 4.

Characteristically, patients while in the shocklike state were conscious, rational and oriented. The pulse was weak, rapid and thready or imperceptible. In many cases the blood pressure was unobtainable. In others it was low with a marked decrease in the pulse pressure. Patients stayed in

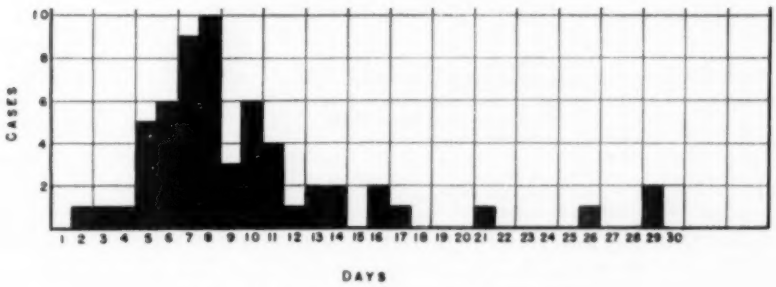



FIG. 12. Duration of disease in 58 fatal cases.

TABLE III

Recorded Clinical Findings and Presence of Necrosis in 57 Fatal Cases

| Duration of Disease in Days | No. of Cases | Shock* | Anuria or Oliguria | Uremia | Pulmonary Edema | Adrenal Necrosis | | Pituitary Necrosis | | Kidney Necrosis | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | + | − | + | − | + | − |
| 2 | 1 | 1 | | | | 0 | 1 | 0 | 1 | 0 | 1 |
| 4 | 1 | | | 1 | | 1 | 0 | 1 | 0 | 1 | 0 |
| 5 | 5 | 5 | 2 | 1 | | 1 | 4 | 1 | 2 | 2 | 3 |
| 6 | 6 | 5 | 3 | 1 | 2 | 1 | 2 | 3 | 3 | 4 | 2 |
| 7 | 9 | 6 | 5 | 4 | 4 | 2 | 7 | 5 | 0 | 8 | 1 |
| 8 | 10 | 8 | 6 | 7 | 4 | 2 | 8 | 3 | 0 | 6 | 0 |
| 9 | 3 | 1 | 3 | 2 | | 1 | 2 | 2 | 1 | 2 | 1 |
| 10 | 6 | 5 | 5 | 3 | 3 | 2 | 4 | 3 | 1 | 4 | 1 |
| 11 | 4 | 2 | 4 | 3 | 1 | 0 | 3 | 1 | 0 | 4 | 0 |
| 12 | 1 | | 1 | 1 | | 0 | 1 | 1 | 0 | 1 | 0 |
| 13 | 2 | 1 | 2 | 2 | 1 | 1 | 1 | 2 | 0 | 2 | 0 |
| 14 | 2 | | 1 | 2 | 1 | 0 | 2 | 2 | 0 | 1 | 1 |
| 16 | 2 | 1 | 1 | 1 | 1 | 0 | 2 | 2 | 0 | 1 | 1 |
| 17 | 1 | 1 | 1 | 1 | | 0 | 1 | | | 0 | 1 |
| 21 | 1 | 1 | 1 | 1 | | 0 | 1 | 1 | 0 | 0 | 1 |
| 26 | 1 | | 1 | 1 | | 0 | 1 | 1 | 0 | 1 | 0 |
| 29 | 2 | | 2 | 2 | 1 | 0 | 2 | 2 | 0 | 1 | 1 |
| Totals | 57 | 37 | 38 | 33 | 18 | 11 | 42 | 30 | 8 | 38 | 14 |

* Cases in which at least one episode of shock is recorded at some time during clinical course.
+ Present.
− Absent.

such shocklike state without alteration in findings for periods ranging from one to 36 hours or more. Some patients had recurrent episodes of shock. In many patients shock was irreversible, and 12 patients died during an episode of shock. Frequently there was hemoconcentration which could not be altered by intravenous therapy, including saline, plasma and whole blood. Shock was an important factor in causing death during the first week of illness (table 5), accounting for 10 of the 23 deaths occurring during

TABLE IV

Immediate Cause of Death as Clinically Recorded in 61 Fatal Cases of Epidemic Hemorrhagic Fever

| | | |
|---|---|---|
| Uremia | | 28 |
| Uremia alone | 19 | |
| Uremia and pulmonary edema | 6 | |
| Uremia and pneumonia | 2 | |
| Uremia and cerebral hemorrhage | 1 | |
| Uremia and shock | | 1 |
| Shock | | 12 |
| Shock alone | 11 | |
| Shock and acidosis | 1 | |
| Pulmonary edema | | 8 |
| Cerebral hemorrhage | | 1 |
| Acidosis | | 1 |
| Suicide | | 1 |
| Unknown | | 9 |
| Dead on arrival at hospital | 3 | |

this time. In addition, there were three patients, dead on arrival at a hospital, who probably died during such an episode.

This shocklike state differed from the typical Waterhouse-Friderichsen syndrome pathologically as well as clinically. Only five of the 12 patients who died in shock showed significant adrenal hemorrhage and necrosis (table 6). On the other hand, similar adrenal changes were found in six patients who did not die in shock. It is suspected that the episodes of shock recorded in the histories of so many of these fatal cases (table 3) may have caused further injury to the already damaged kidney.

Renal failure was the major cause of death after the first week of disease (table 5). All patients, including those who survived the disease, showed some evidence of renal involvement. This evidence consisted of occult hematuria, albuminuria and cylindruria during the early stages of the illness, and this frequently preceded other hemorrhagic manifestations. The more seriously ill patients and those who died of the disease showed evidence of

TABLE V

Correlation of Immediate Cause of Death and Duration of Disease

| Duration of Disease in Days | No. of Cases | Uremia | Uremia and Shock | Shock | Pulmonary Edema | Cerebral Hemorrhage | Acidosis | Suicide | Not Recorded* |
|---|---|---|---|---|---|---|---|---|---|
| 1–7 | 23 | 5 | | 10 | 5 | | 1 | | 2 |
| 8–14 | 28 | 18 | | 2 | 2 | 1 | | | 5 |
| 15–21 | 4 | 2 | 1 | | 1 | | | | |
| 21+ | 3 | | | | | | | | |
| Unknown | 3 | | | | | | | 1 | 2 |
| Total | 61 | 28 | 1 | 12 | 8 | 1 | 1 | 1 | 9 |

* Three patients dead on arrival at hospital included two with known duration of less than seven days and one of unknown duration.

renal failure, except for the small group who died early in the disease during a period of shock. The clinical evidence of renal failure included oliguria, anuria and azotemia. If the patient survived this he developed polyuria, with a daily output of 5,000 to 6,000 c.c. of urine of low fixed specific gravity. In fatal cases reaching this stage the polyuria had no effect on the azotemia.

Pigmented casts were found in many of the kidney sections, indicating the presence of lower nephron nephrosis. In most cases, however, an interstitial cellular infiltrate about degenerating tubules was lacking. It is suspected that the lower nephron nephrosis was a complication related to the episodes of shock. Much more prominent was the medullary hemorrhage and necrosis. This was so characteristic that the term "EHF kidney" could well be used. Since there was evidence of renal involvement clinically very early in the disease and since even the cases of shortest duration showed renal damage regardless of the immediate cause of death, it is evident that

the kidney is at least one of the organs primarily affected. The restriction of the changes to the renal medulla is not easily explained. Further, it is difficult to explain the type and location of necrosis in the renal medulla and the similar necrosis primarily affecting endocrine tissues, including the anterior lobe of the pituitary and the adrenals. These lesions are correlated with the two major causes of death, shock and uremia, in tables 6 and 7.

Only occasionally were the hemorrhagic features of the disease a direct cause of death. Two patients had gross cerebral hemorrhages, and one patient had a subdural hemorrhage. Other patients lost sufficient blood by hemorrhage from the gastrointestinal tract to require transfusion as replacement therapy. However, no patient died in shock from blood loss, and in few patients was there evidence that the shock was related to hemorrhage.

As indicated in the description of pathologic changes, hemorrhage could occur in any tissue or organ. However, hemorrhage was almost constantly found in the right atrium, gastrointestinal mucosa, kidney medulla, submucosa of renal pelvis, peripelvic fat, subconjunctival tissues and skin of

TABLE VI

Correlation of Necrosis of the Adrenals, Pituitary and Kidneys in 12 Patients Who Died in Shock

| Duration of Disease in Days | No. of Deaths | No. Dying in Shock | Adrenal Necrosis | | Pituitary Necrosis | | Kidney Necrosis | |
|---|---|---|---|---|---|---|---|---|
| | | | + | − | + | − | + | − |
| 1–7 | 23 | 10 | 4 | 6 | 5 | 3 | 7 | 3 |
| 8–14 | 28 | 2 | 1 | 1 | 0 | 1 | 2 | 0 |

trunk and upper extremities. The skin at pressure points and the conjunctivae and gastric mucosa during vomiting were areas subject to irregular variations of stress and strain, and in some of these areas, notably the conjunctivae, hemorrhages have been observed to occur during such periods of stress. In other locations, such as the heart and kidney, this does not appear to be an adequate explanation. Since the hemorrhage generally appeared related to vessels of the smallest size, and because of other evidence mentioned of capillary dysfunction, it is believed that the hemorrhage reflected a generalized alteration in capillary physiology. No consistent morphologic evidence of alteration of the capillaries or small vessels was found.

Several features have not been discussed because observations were incomplete. Morphologically, there was definite evidence of cardiac involvement. However, cardiac failure was not recorded as such in clinical records. It was observed that patients recovering from periods of prolonged shock and some entering the phase of polyuria tended to develop pulmonary edema. Other patients developed pulmonary edema when too vigorous intravenous therapy was instituted. Table 4 shows that eight patients died of pulmonary edema and six others of uremia and pulmonary edema. It is suspected that

at least some of these patients died of myocardial failure, and that in treatment the possibility of such cardiac failure must be considered.

The necrosis seen frequently in the kidneys and anterior lobe of the pituitary suggested that patients who have had a serious but not fatal attack may subsequently show permanent residual renal or pituitary dysfunction. It should be noted that although fixed low urinary specific gravity has been found to persist for several months, Russian investigators [2] report that after recovery there are no permanent residual changes.

Several clinicians reported the presence of hyperpigmentation of the head and neck resembling a bronzing or mild sunburn, and others noted a mild, superficial, easily missed macular rash involving the upper part of the body during the first few weeks of the disease, followed by a branny desquamation during the later stages. Skin sections showed a diffuse superficial dermatitis, but this could not be further characterized because the sites of these skin sections and the relation to a rash were not known.

It was usual for patients with epidemic hemorrhagic fever to have persistent, frequent vomiting. Undoubtedly this was so severe that there was

TABLE VII

Correlation of Necrosis of the Adrenals, Pituitary and Kidneys in 28 Patients Who Died in Uremia

| Duration of Disease in Days | No. of Deaths | No. Dying in Uremia | Adrenal Necrosis | | Pituitary Necrosis | | Kidney Necrosis | |
|---|---|---|---|---|---|---|---|---|
| | | | + | − | + | − | + | − |
| 1–7 | 23 | 5 | 1 | 3 | 2 | 1 | 3 | 1 |
| 8–14 | 28 | 18 | 3 | 12 | 11 | 0 | 12 | 2 |
| 15–21 | 4 | 2 | 0 | 2 | 1 | 0 | 1 | 1 |
| 21+ | 3 | 3 | 0 | 3 | 3 | 0 | 2 | 1 |

a marked physiologic effect, with alteration of acid-base balance and blood volume. The rôle of vomiting in the pathogenesis of the lesions of epidemic hemorrhagic fever could not be assessed morphologically. However, it was believed that the esophagitis was a reflection of chemical damage.

The character of the cellular infiltrate in the heart and interstitial tissue of the pancreas, the cellular reaction in the spleen, liver and peripheral blood, and the lack of cellular reaction in the areas of necrosis appear to be peculiar to epidemic hemorrhagic fever. The distribution of lesions, the prominence of mononuclear cells and the lack of suppuration are interpreted as supporting the theory of a nonbacterial cause of this disease and the possibility that the etiologic agent is a rickettsia or a virus. However, neither the site of introduction nor the site of propagation of such an agent has been recognized.

The following tentative hypothesis has been formulated to explain these observations. It is suggested that whatever the etiologic agent may be, a toxic agent is introduced into the blood stream which produces a marked

alteration in capillary function, and to which certain specific sensitive tissues react by direct coagulation necrosis. It is further suggested that the renal medullary necrosis reflects areas of concentration of the toxic agent, being excreted in the renal tubules, and that the shocklike states are evidence of reactions of the individual to large amounts of circulating toxin. Further observations, study and experimentation are undoubtedly required to afford a better understanding of epidemic hemorrhagic fever, its etiology, pathogenesis and treatment.

## Summary

1. The disease epidemic hemorrhagic fever, occurring in UN troops in 1951 in Korea, was found to be identical with the disease described by the Japanese in Manchuria and probably identical with a disease described by the Russians in Siberia.

2. The etiologic agent causing epidemic hemorrhagic fever is unknown but is probably a rickettsia or a virus.

3. The clinical picture in epidemic hemorrhagic fever in fatal cases is characteristic.

4. The characteristic pathologic features as observed in the autopsies of 61 fatal cases are described. Three features are prominent: hemorrhage, particularly in the renal medulla, right atrium and submucosa of the gastrointestinal tract; a peculiar type of necrosis of the renal medulla, anterior lobe of the pituitary, adrenal, and occasionally of islands of Langerhans; and a mononuclear cellular infiltration of the myocardium, pancreas, spleen and liver. The renal changes are so unusual as to deserve the descriptive title of "kidney of EHF."

5. The abnormal physiologic processes are not entirely understood, but it is evident that shock causes many of the deaths during the early stages of the disease, and that thereafter renal failure is the important cause of death. The rôle played by protracted vomiting and by cardiac and endocrine involvement is undetermined. It is believed that an alteration in capillary physiology is a fundamental process.

6. Neither the site of entrance nor the site of propagation of the etiologic agent is recognized. It is suspected, however, that the pathologic changes in fatal cases are produced by a potent circulating toxic agent acting on capillaries, renal medulla and certain portions of endocrine glands.

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# CLINICAL ASPECTS OF THE RENAL PHASE OF EPIDEMIC HEMORRHAGIC FEVER*

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The early acute phase of epidemic hemorrhagic fever has been discussed in earlier papers. Our experience with this disease has been limited almost completely to the later phase, following the drop of the temperature to normal. I plan to discuss briefly certain aspects of this later, or renal phase of hemorrhagic fever.

The majority of almost 300 patients seen at this hospital can be classed as moderately severe. In these individuals, at about six days after onset of illness, the temperature is normal, abdominal and low back pain are still present, and there is frequently hiccoughing and vomiting. There is evidence of bleeding—frequently epistaxis, subconjunctival hemorrhages, petechiae and guaiac positive stools. There is very often a puffiness of the upper eyelids. The urine still contains red blood cells, albumin and often some hyaline or granular casts. The volume of urine in this group of patients may be somewhat diminished, but is usually at least 800 c.c. daily, and it is not grossly bloody. The blood non-protein nitrogen and urea nitrogen may be moderately elevated up to 50 to 70 and 20 to 30 mg. per cent, respectively. The blood pressure is frequently slightly elevated at this time, 140–150/90 mm. Hg. Then there is a rapid change, occurring usually between the seventh and ninth days of disease. There is a diuresis, with disappearance of albumin and later of red blood cells from the urine, with rapid disappearance of periorbital edema. The abdominal pain subsides rather rapidly, the back pain more slowly, and the patients become extremely hungry. By the twentieth day there is frequently no nitrogen retention, but the urine specific gravity remains low.

There is a smaller group of patients that are more severely ill, who present a somewhat similar clinical picture at the end of the first week of illness, but whose subsequent course differs markedly. Subjective symptoms are often no more severe, in fact several of the more seriously ill patients stated they had very little abdominal or back pain. Drowsiness, disorientation, delusions, violent behavior, purposeless movements and even complete unconsciousness, however, are common. They are also weak, dehydrated, acidotic and oliguric—or completely anuric. The hematocrit is often over 60 (in one-fourth of the 12 most seriously ill patients), the mouth and pharynx caked with dried secretion and blood, and the skin lacking in normal turgor. The extremities are apt to be cold and blue, though the blood

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pressure is above normal. The effect of hemoconcentration of this order on any kidneys may be disastrous, but may be especially significant in these patients whose kidneys are already insulted. Acidosis is indicated by a low blood carbon dioxide, below 40 vol. per cent in 10 of 15 severely ill patients. Salt depletion is probably an additional significant factor in contributing to the clinical state during the renal phase of hemorrhagic fever. Serum sodium determinations were made in three patients who subsequently died, and in each instance (260, 312 and 291 mg. per cent; normal 315 to 350), the value was significantly below normal. Serum chlorides were almost uniformly low, but not due entirely to vomiting, in view of the low $CO_2$ and Na. This can probably be accounted for by salt lost in the urine due to diminished tubular reabsorption, and to inadequate intake of sodium chloride. It is of interest that three patients spontaneously requested additional salt on their food as soon as they began to eat again.

The Thorne test was done on eight seriously ill patients, either before or just after the time diuresis occurred. This ranged from the sixth to twenty-first day of disease. Circulating eosinophils were counted twice using the Phloxine in propylene glycol method before the injection of 40 mg. of ACTH, then at hourly intervals for four hours. In no instance was there a significant drop (50 per cent or more) in circulating eosinophils following injection of ACTH. It can only be surmised that the adrenal hypofunction so indicated is due to adrenal exhaustion or actual adrenal damage from hemorrhage or to atrophy secondary to pituitary damage. In several autopsy reports adrenal hemorrhages or cortical thinning has been noted. Adrenal cortical failure probably contributes to the now familiar clinical picture.

In correcting the dehydration, salt depletion and adrenal cortical hypofunction, there is the hazard of overloading the circulation and causing pulmonary edema or right ventricular failure or both in the presence of diminished urine output. That this is a very real danger is shown by chest x-rays of five patients taken during an episode of actual pulmonary edema or congestion. In each instance this was the initial x-ray taken after admission, and there was no correlation with parenteral fluid administration. X-ray of the chest, taken seven to 11 days after the onset of disease in five patients, showed definite cardiac enlargement in four and definite pulmonary congestion in five. There was a small pleural effusion in two. The pulmonary abnormalities interpreted as congestion were an increase in vascular markings, and hilar and perihilar densities which ranged from a blotchy appearance, to being massive throughout the lower lung fields. It is possible that azotemia contributed to the blotchy densities. In only two patients was there definite clinical evidence of pulmonary edema—namely, wet râles and rhonchi. These two individuals also had elevated venous pressure, and slight ankle and sacral edema indicating right heart failure as well. Repeat x-rays of the chest, taken two to seven days after the initial one, revealed

normal heart size and clear lung fields in four of these individuals. The fifth patient when examined radiographically two days after the initial film, when there were no physical signs of decompensation, demonstrated partial clearing of the lung fields. He died four days later without recurrence of pulmonary edema.

So it was with some apprehension that eight seriously ill patients were treated with large amounts of cortisone, and more parenteral sodium chloride than had been used previously. It was thought that the salt and water retaining effect of cortisone might precipitate pulmonary edema, but such was not the case. (Three patients will not be considered here because of insufficient time for follow-up.) The following plan was adhered to: parenteral fluid was given slowly intravenously, in an amount equal to the volume of urine and vomitus in the preceding 24 hours plus 600 to 1,000 c.c. One half of the parenteral fluid was normal saline or one-sixth molar sodium lactate. If the hematocrit was high, larger amounts of fluid were given. Cortisone was given intramuscularly, 200 mg. initially, then 100 mg. daily in a single injection for six to 10 days, followed by three days of tapered dosage. If the patient was in shock, plasma was given. If there was appreciable bleeding apparent, whole fresh blood was given, usually after withdrawing 300 to 400 c.c. blood from the patient.

Five patients so treated are compared with five equally ill patients who received considerably less saline and no cortisone, and with five patients who likewise received less saline and no cortisone, but who died. All of these patients were admitted to the hospital between the third and thirteenth days of disease, the average for each group of five being the sixth day of disease. At least three in each group had grossly bloody urine, all 15 were oliguric and almost all had been in "shock" at some time during their illness. A daily urine output of less than 1,000 c.c. occurred for two, three, and four days (average for each group of five patients). All were semi-stuporous or completely comatose during most of the second week of disease. Two had generalized convulsions. The maximum blood non-protein nitrogen and urea nitrogen attained, uniformly at the end of the second week of disease, were remarkably similar in the three groups of patients, the average for each group being between 134 to 150 mg. per cent non-protein nitrogen, and 88 to 98 mg. per cent blood urea nitrogen. The average maximum creatinine ranged from 6.8 to 8.7 mg. per cent and the minimum $CO_2$ from 28.4 to 40.4 vol. per cent. The five patients who died did so between the thirteenth and seventeenth days of disease. The non-protein nitrogen and blood urea nitrogen had returned to normal by the twenty-third day in the patients who received cortisone, and by the fortieth day in those who did not. It is impossible to compare the duration of reduced concentrating ability because not enough time has yet elapsed. Serum sodium determinations made in three patients after two to three days of treatment with cortisone and saline were within normal limits, whereas serum sodium was definitely low in three patients not so treated who subsequently died. There was no significant

difference in the blood pressure elevation or duration of abnormal blood pressure in the treated and untreated patients. There was no increase of apparent edema in any patient who received cortisone.

Although no dramatic difference is evident, it seems physiologically sound to correct as much as possible dehydration, salt depletion and adrenal hypofunction when present. It is pointed out that no untoward effects were apparent from the steps taken to correct electrolyte and fluid imbalance.

When diuresis occurs at the end of the second week or during the third week in those severely ill, or by the middle of the second week in those moderately ill, there is a rather abrupt clinical improvement. The urine produced, however, is of low specific gravity and this is maintained for a variable number of weeks. That this is a result of diminished tubular reabsorption, not to a lack of pituitary anti-diuretic substance, is shown by a concomitant failure to excrete phenolsulfalein (PSP) at a normal rate. Further evidence that it is due to tubular hypofunction is the absence of evidence incriminating the glomeruli. The urea clearance test is perfectly normal, and there is no impairment in the ability to secrete urine of a specific gravity below 1.010. The conclusion that tubular function of the kidney is affected primarily is borne out by examination of the kidneys after death.

The duration of tubular hypofunction is of some importance. As measured by the concentration test and PSP test, months may elapse before there is a return to normal. Six patients have been followed four months since onset of disease. All but one were severely ill. Without exception these individuals had abnormal PSP or urine concentration tests two months or more after onset of illness. By four months from onset the PSP test was normal in five and the specific gravity of a casual specimen of urine was at least 1.020 in five. Many other patients have similar evidence of tubular dysfunction, at least two months after the onset of disease, but follow-up is too short to make any further statements. It is noteworthy that there is not complete correlation between the degree of renal abnormality during the acute illness and the duration of tubular hypofunction. The symptoms of nocturia, diurnal frequency and increased thirst accompany the laboratory evidence of water and salt wasting. It cannot yet be stated that the tubular damage is always completely reversible in individuals who survive.

# EPIDEMIC HEMORRHAGIC FEVER: A SUMMARIZATION *

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## Introduction

It is not often in a medical career that one has the opportunity to participate in the investigation of the clinical pattern of a new disease entity. That opportunity, fortunately or unfortunately, was given by circumstances to the doctors of the Medical Services of the Far East Command. Needless to say, it has been seized with an awareness of the potentialities involved, and the investigators have worked long and hard. The results have been presented in the preceding symposium.

The work was most fortunately begun with a ready-made background supplied by the Japanese investigators of a decade ago. At first the effort was necessarily sporadic and more on the basis of opportunity than protocol, as is true in the presence of all new and hazily recognized entities. As the problem to be dealt with became clearer the work assumed more orderly fashion, and organized projects were undertaken to supplement individual effort. The first of these projects was the epidemic hemorrhagic fever laboratory set up in a quiet rear sector of Korea, in a hospital easily accessible to the endemic area. The staff was chosen from amongst the experienced investigators of the command, and they have carried on an intensive detailed study of the symptoms, signs and clinical laboratory findings in a limited number of cases. To complement this more detailed work a gross statistical study was organized in Japan, to which country, because of the military situation, the bulk of the cases were evacuated. In addition, a study of the effects of convalescent serum has also been organized. Future plans have been made for a more intensive study of therapeutic possibilities in the event of another outbreak. Although it is yet too early to give conclusive results, the need for early information has inspired this symposium.

## Definition

Epidemic hemorrhagic fever is an acute, fulminating, often fatal, otherwise self-limited disease of unknown etiology, characterized by severe toxemia, widespread capillary damage, and hemorrhagic diathesis, with resulting symptoms, signs and sequelae thereof, particularly renal involvement.

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This presentation is a necessarily brief summarization of the papers presented at the Symposium on Epidemic Hemorrhagic Fever, interpreted in the light of personal experience and thought. Much detail has been omitted in the interest of brevity.

## Etiology

The etiology can be dismissed with the statement that the cause, vector and conditions necessary for transmission at this time are unknown. The illness does not appear to be contagious.

## Pathology

The gross and microscopic pathology is that of hemorrhage and its end results. The hemorrhage may be both petechial and gross, bizarre in its manifestations and widespread throughout the body. The most constant and outstanding findings are in the kidney, heart, gastrointestinal tract and lungs. In the kidney the hemorrhage is severe, intense, and limited almost entirely to the medullary pyramids, and is associated with extratubular packing of red blood cells and a peculiar necrosis within those pyramids. The renal pelves show marked submucosal hemorrhage demarcated sharply at the ureteropelvic junction. The heart shows petechial involvement throughout but no valvular or coronary damage. The most startling finding is an intense subendothelial hemorrhage limited to and involving the right auricle. The myocardium of both the right and left auricles shows diffuse hemorrhage and interstitial edema. The ventricles are less involved. The gastrointestinal tract shows both petechial and gross hemorrhage as well as intense congestion throughout its length. Strangely enough, the liver, spleen and pancreas show little significant involvement. The lungs show intraalveolar hemorrhage and interstitial fluid accumulation. The pleurae seem to escape damage. The central nervous system, although less frequently involved, may show petechial hemorrhage, congestion and, in rare instances, gross hemorrhage. The meninges may be congested. The pituitary and adrenal glands often show hemorrhage, sometimes focal necrosis. Bone marrow and skin do not show significant findings. For emphasis, it should be restated that any organ or tissue may be involved to almost any degree, and the pathologic findings are characteristic.

## Clinical Findings

The clinical findings of the disease fall easily into three phases, labeled by Powell as invasive, toxic and convalescent. The incubation period is unknown but seems to be somewhere in the range of seven to 30 days, as determined by the patient's arrival in or departure from the endemic area. The average is 12 days.

### Invasive Phase

The symptoms of the invasive phase are chiefly those of systemic reaction to the growth of any offending organism within the bodily economy, in this instance due to a particularly virulent agent to which certain previously unexposed races seem to have little or no natural immunity. Onset is abrupt,

often initiated by a chill, and accompanied by severe frontal or supraorbital headache, backache and generalized muscular aches. Abdominal discomfort occurs early and is accompanied by vomiting, and both gradually increase in severity. The eye symptoms are particularly characteristic in that there is retrobulbar ache, pain on eye movement, blurring of vision and photophobia.

The patient appears acutely ill, and is restless and often prostrate even in this early phase. There is a characteristic flush of varying intensity involving the face, neck and upper chest, suggesting somewhat that seen in crush injury. Sclerae are injected and there may be infraorbital edema. Cervical, axillary and inguinal nodes are moderately enlarged and nontender. Abdominal tenderness is prominent, and costovertebral angle tenderness is a constant finding. The temperature ranges from 100° to 106° Fahrenheit, reaching a peak on the third or fourth day after onset, and falling by lysis on the fourth to seventh day. Pulse is slow, and not at all in proportion to the fever. Blood pressure is at first normal, then rapidly lessens and may reach shock levels.

Early laboratory findings are not at all characteristic. Blood counts, sedimentation rates, platelet counts, bleeding time, coagulation time, prothrombin time and blood chemistries are all essentially normal. After the third or fourth day, however, marked changes take place. The white cell count becomes suddenly elevated and the differential count shows a shift to the left. Sedimentation rate rises, platelet count drops, and bleeding time becomes prolonged. Like the blood, the urine is at first essentially normal, then shows hematuria and 4 plus albumin, and often casts. These changes herald the second, or hemorrhagic, phase of the disease.

### Hemorrhagic Phase

The toxic, or hemorrhagic, phase usually lasts through the tenth to fourteenth day. The patient feels worse, although headache, eye symptoms and muscle aches abate somewhat. However, abdominal pain and lumbar ache become more marked, and protracted vomiting sets in. Hiccoughs are often distressing. The patient is apprehensive, and weakness is prominent. There may be severe cough, hemoptysis and dyspnea. Bloody vomitus is frequent, and diarrhea, when it occurs, is apt to be hemorrhagic.

The patient appears more seriously ill and is markedly restless and often disoriented. Convulsions and delirium may ensue; prostration is marked. Hemorrhagic manifestations now appear, ushered in by a positive Rumpel-Leede test. The scleral injection becomes frank hemorrhage, often so extensive that the sclerae are entirely bright red. Retinal hemorrhages do not occur. There is accompanying periorbital and conjunctival edema. Petechiae are numerous, and are centered in the axillary folds and upper lateral thoracic walls. Marked ecchymoses appear from needle punctures and bruises. The flush of the upper part of the body deepens, so that the

patient often appears sunburned. The adenopathy remains and is now characterized by tenderness. The lungs may or may not show signs of pulmonary engorgement. The heart likewise may or may not show evidence of myocardial involvement. There is often cardiac dilatation and, in some cases, myocardial failure. Blood pressure may be at shock level, and the pulse becomes rapid and of poor quality. When shock occurs, it may last as long as 36 hours. Abdominal and costo-vertebral angle tenderness increases. Subcutaneous and underlying tissues have a "boggy" feeling. Urine becomes increasingly scanty, to the point of oliguria and in some cases anuria.

The laboratory findings become more significant. The white blood count averages 30,000 to 40,000, with counts up to 93,000 reported. The differential count shows a sharp shift to the left, often with a leukemoid reaction. Atypical lymphocytes are present, and occasionally eosinophils appear in small numbers. The sedimentation rate increases sharply, often to levels of 40 mm. per hour (Westergren). There is an apparent hemoconcentration, as manifested by markedly increased hematocrit readings. Platelet counts, which are low, rebound soon to normal levels, and bleeding time returns to normal. Prothrombin time is not appreciably altered. Bone marrow is not remarkable; liver function studies and the usual agglutination tests are within normal range. Serum bilirubin levels are not significantly increased.

The urine, which has shown hematuria and albuminuria, now clears and the volume becomes scant, with low specific gravity. Urinary chlorides are reduced; phenolsulfonphthalein function test is low. Non-protein nitrogen rises, rapidly reaching, in all cases, levels above 100 mg. per cent and often above 200 mg. per cent. Blood creatinine rises correspondingly. Blood chlorides decrease moderately, and there is a fairly consistent decrease in the $CO_2$ combining power to between 30 to 40 vol. per cent.

### Convalescent Phase

During the convalescent phase, which lasts for from three to six weeks, the symptoms disappear more or less rapidly, as do the hemorrhagic phenomena. The conjunctival hemorrhages remain longest, fading slowly through stages which at times resemble icterus. Weight loss is regained slowly, even though appetite may be voracious. Patients complain particularly of muscular weakness, intention tremor and lack of stamina. These too gradually disappear. Non-protein nitrogen comes down slowly as the recovery phase of lower nephron nephrosis ensues, with its polyuria and gradually increasing specific gravity. Blood pressure may be slightly elevated but the cardiovascular system is otherwise normal. Blood counts, sedimentation rates, platelet counts, bleeding time, all return to normal early in the convalescent phase. Phenolsulfonphthalein excretion may be low temporarily, but this too soon returns to normal.

## Prognosis

Prognosis is favorable for both recovery and the escape from residuals. Mortality rate at the time of this writing, including the early phases where only the severe cases were recognized, is just below 7 per cent. Death occurs most often between the fifth and eleventh days, the seventh and eighth days showing the peak of incidence. Death is due to uremia, toxemia, gross hemorrhage, cardiac failure, pulmonary edema, shock, exhaustion, electrolyte imbalance, or any combination thereof. Deaths which occur after the toxic phase are basically due to uremia and have occurred as late as the twenty-ninth day after onset. For the 93 per cent who recover, convalescence proceeds at varying paces; the milder cases have been returned to duty in as little as five weeks. At the present, all cases have recovered without detectable residuals and recurrences have not been reported.

## Diagnosis

In the light of our present knowledge, the following criteria seem necessary for diagnosis: The patient must have been in the endemic area, presumably within the stated incubation period, and there must be characteristic history, hemorrhagic findings and evidences of renal involvement. The condition has been mistaken for leptospirosis, hemorrhagic malaria and typhus. Diagnosis is difficult prior to the onset of the hemorrhagic phase.

## Treatment

Specific therapy has not yet been determined, although almost the complete spectrum of applicable drugs has been exhibited. The most successful management seems to be bed-rest, good nursing care, symptomatic relief and sedation. Symptomatic relief requires the closest evaluation of every manifestation. Shock must be combated as effectively as possible. A word of caution is in order concerning correction of fluid and electrolyte imbalances. Although the patient may early appear dehydrated, experience has shown that even small amounts of fluid intravenously may throw the patient into pulmonary edema. It is therefore better to give oral fluids when possible, rectal drip or small amounts of subcutaneous fluids otherwise. Cautious correction of the chloride deficiencies and the acidosis is of great value, keeping in mind the dangers noted above. The polyuric phase of recovery, with its attendant electrolyte imbalances, can be dealt with appropriately inasmuch as the danger of pulmonary edema subsides with the disappearance of the hemorrhagic manifestations.

Sedation is of the utmost importance, giving whatever drug seems indicated. Barbiturates do not seem contraindicated. Narcotics give the best results, effectively overcoming pain, restlessness and agitation. They are most useful in combating the severe cough and the retching, both of which should be controlled as they appear to predispose to the more serious com-

plications. The cases sedated early, thoroughly and throughout the severe phases of the disease appear to do the best.

Although claims have been made for success in early administration of both whole blood and convalescent whole blood, these cannot be substantiated. Neither have the claims made in this symposium for Benadryl therapy been substantiated.

## Pathologic Physiology

Speculative writing is not often indicated in medicine. However, the number of unknowns and the unusual situation presented by this disease seem to justify contemplation as to the mechanisms of the pathologic physiology. A disease entity new to the Western world of medicine, acute, severe, and with an appreciable mortality rate, requires an attempt at explanation.

It is entirely possible that this disease is caused by a virus which has an affinity for the endothelial cells of the cardiovascular tree. In the viremia stage, this organism could produce the severe systemic reaction which characterizes the invasive phase. By the time immunity has developed to the point of successfully combating the organism, cellular invasion has produced cellular damage, which in turn results in the capillary fragility which characterizes the hemorrhagic phase. By the time the endothelial cells have regenerated sufficiently to reëstablish the integrity of the capillary tree, the hemorrhagic manifestations and their attendant findings have receded and one is left with only the end results of the toxemia and the hemorrhages. These, too, gradually return to normal without significant residuals.

In proposing this virus theory, which, incidentally, is entirely in accordance with the early Japanese writings, one cannot totally disregard the possibilities that the capillary damage may be produced by a toxin arising from some other type of organism or some allergy or metabolic disturbance. Although rickettsia have not yet been isolated, many of the manifestations of the disease suggest rickettsial involvement. Admittedly, therapeutic failures point away from this supposition. Likewise, one cannot disregard the similarity between the widespread capillary damage of this condition and that of acute rheumatic fever. Neither can one completely ignore the speculations reported in this symposium concerning the possible rôle of histamine. It still remains for the laboratory investigators to give us the answer to the causative organism.

Regardless of what organism or mechanism may cause the capillary damage, the key to the situation seems to be the capillary fragility engendered. This would explain the petechiae, the ecchymotic findings, the varying degrees of widespread hemorrhage and the findings resembling acute glomerular nephritis. The low platelet count and the prolonged bleeding time are part and parcel of this picture. The capillary damage could also explain the early transudation of fluid into the tissue spaces. More specifically, the persistent abdominal pain may be accounted for by the varying degrees of hemorrhage into the organs within the peritoneal cavity, much as that seen in hemor-

rhagic purpura. The escape of plasma into the retroperitoneal tissues may also add to the picture. The costovertebral angle ache may be due to involvement of the kidney and contributed to by the involvement of the perirenal and retroperitoneal tissue. The cardiovascular manifestations may be accounted for by hemorrhages into the cardiac structures, plus the interstitial edema of the myocardium. The pulmonary findings seem to be of capillary origin but may be due to larger hemorrhage plus the fluid accumulation incident to plasma transudation. Cardiac failure complicates the picture; the cardiopulmonary balance may be so critical that small amounts of intravenous fluid may produce pulmonary edema. The headache, restlessness, irritability and coma could be accounted for by petechial hemorrhages, congestion and edema of the central nervous system. Involvement of the basilar areas (pituitary hemorrhage is often noted) would account for the ocular symptoms. Capillary fragility aggravated by the effort expended in retching and coughing could account for the gross hemorrhages seen in the various organs and bodily sites. One of the workers (Barbero) has observed the development of scleral hemorrhages following severe bouts of retching. Shock may also be a contributing factor.

The renal physiology is most intriguing. The urinary findings which so closely resemble acute glomerular nephritis can be accounted for by glomerular capillary fragility. These glomerular manifestations recede promptly with capillary repair. In passing, it should be noted that hematuria and albuminuria are not present in the earliest phases, prior to the onset of damage to the endothelial cells. The tubular injury which results in the varying degrees of oliguria can be accounted for by damage to the tubular epithelium secondary to anoxia, which, in turn, may be the result either of the intense packing of hemorrhagic products in the extra tubular spaces of the medullary pyramids, or of the shock blood pressure levels of prolonged duration. Perhaps both mechanisms contribute to the picture. Animal experimentation has shown significant tubular epithelial damage in complete anoxia of two hours' duration, or partial anoxia of longer periods.

Admittedly, the very brief and unelaborated explanations proposed above are not all-encompassing. If there is widespread capillary fragility with petechial hemorrhages throughout, why are there no manifest retinal hemorrhages? Also, why are the liver and spleen so sparingly affected? And why are the selectively heavy subendothelial hemorrhages limited sharply to the right auricle or the selectively heavy submucosal hemorrhages limited sharply to the renal pelvis? Further, why is there heavy hemorrhage in the medullary portions of the kidney while the cortex is almost blood free? And if this is a viremia, why the unusually high leukocyte counts? These and many other similar objections demand more adequate explanation. Perhaps these explanations will become more apparent as the work progresses.

# CASE REPORTS

## LOEFFLER'S SYNDROME FOLLOWING PENICILLIN THERAPY *

By SEYMOUR REICHLIN, M.D., *St. Louis, Missouri*, MARY H. LOVELESS, M.D., and ERNEST G. KANE, M.D., *New York, N. Y.*

THIS case of Loeffler's syndrome is reported because it demonstrates the production of marked pulmonary infiltration and eosinophilia following sensitizing doses of a penicillin preparation. Although an allergic basis has been postulated for Loeffler's syndrome, there are few cases in the literature which demonstrate clearly a temporal relation to a specific allergen.

### CASE REPORT

A 26 year old white college student first entered New York Hospital on November 18, 1950, with a chief complaint of cough and fever of six hours' duration. He had been in good health prior to this illness. Two years previously he had had a mild sore throat, which was treated by penicillin lozenges. In September, 1950, on routine examination, a positive serologic test for syphilis was found, but complete examination including chest x-ray was negative. Four weeks prior to admission he began taking injections of procaine penicillin in sesame oil with 2 per cent aluminum monostearate at approximately semiweekly intervals at an outside clinic. Following the fourth injection, he developed localized soreness and swelling and general weakness for two days. After the fifth injection, a similar localized reaction occurred and was

TABLE I

Course in Hospital

| Date | Total WBC | Eosin. % | Lymph. % | Mono. % | Bas. % | Neutrophiles | |
|---|---|---|---|---|---|---|---|
| | | | | | | Mature % | Band % |
| Nov. 18 a.m. | 23,150 | 4 | 8 | 2 | 0 | 76 | 10 |
| Nov. 18 p.m. | 22,000 | 16 | 22 | 2 | 0 | 53 | 7 |
| Nov. 19 | 30,200 | 38 | 19 | 2 | 1 | 30 | 10 |
| Nov. 20 | 27,800 | 50 | 20 | 1 | 0 | 27 | 2 |
| Nov. 21 | 29,300 | 51 | 19 | 0 | 0 | 26 | 4 |
| Nov. 22 | 41,500 | 68 | 16 | 2 | 0 | 12 | 2 |
| Nov. 24 | 42,900 | 80 | 7 | 0 | 1 | 11 | 1 |
| Nov. 25 | 45,900 | 78 | 6 | 3 | 0 | 12 | 1 |
| Nov 26 | 42,900 | 74 | 9 | 0 | 0 | 21 | 5 |
| Nov. 28 | 25,700 | 55 | 18 | 0 | 1 | 23 | 3 |
| Nov. 29 | 13,700 | 47 | 19 | 4 | 0 | 26 | 4 |
| Nov. 30 | 13,700 | 34 | 19 | 6 | 1 | 37 | 3 |

* Received for publication May 11, 1951.

From The New York Hospital and the Department of Medicine, Cornell University Medical College, New York, N. Y.

followed in about one hour by generalized urticaria. The eruption responded to 50 mg. of tripelennamine hydrochloride orally. The sixth injection a week later, given 20 minutes after a dose of tripelennamine hydrochloride, elicited no reaction of any sort. He again took the antihistaminic before the seventh injection but nevertheless became very weak and developed a dry sore throat and a painful, burning paroxysmal cough a few minutes later. There was no fever, skin manifestation or wheezing. The episode lasted for about two days, gradually abating. On the day of admission, he again had an injection of penicillin, preceded by tripelennamine hydrochloride as before. Within an hour of the injection he developed severe burn-

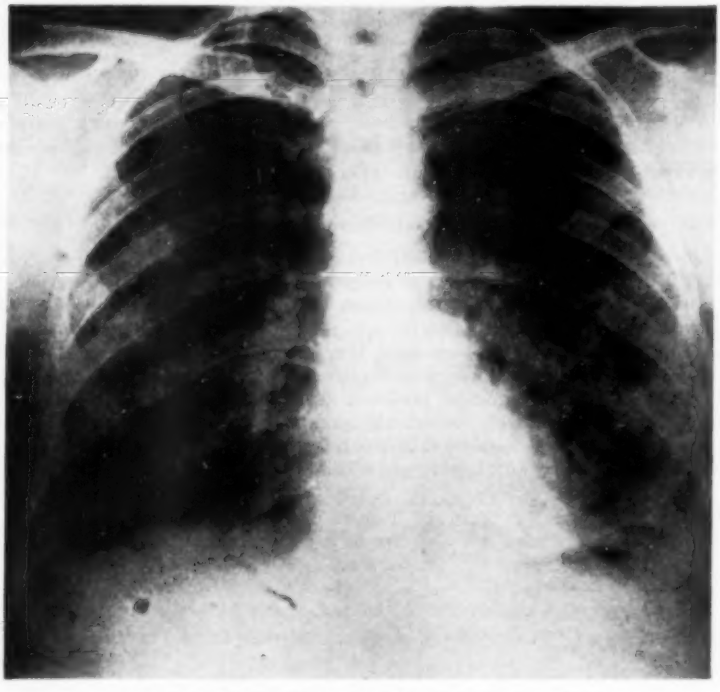


FIG. 1. Roentgenogram of November 19, 1950.

ing and soreness of the throat, cough, chills and fever, and throbbing headache. Six hours later he presented himself for admission.

The patient had had mild hay fever in childhood, but there was no other personal or familial allergic disease.

*Physical Examination:* Physical examination revealed a temperature of 39.6° C. (103.2° F.); pulse, 104; respirations, 20; blood pressure, 138/78 mm. of Hg. The patient was a well developed young adult male who appeared moderately ill. He was flushed, and had slight dermographia and a frequent dry, nonproductive cough. Minimal involvement of toes by epidermophytosis was noted. There were small, nontender nodes in each axilla and groin, and occasional and variable scattered crepi-

tant râles were heard in the chest. The remainder of the findings were within normal limits.

*Admission Laboratory Data:* The findings were as follows: white blood count, 23,150 (per cu. mm.), with 8 per cent lymphocytes, 2 per cent monocytes, 76 per cent neutrophils, 10 per cent stab forms, 4 per cent eosinophils. Red count, hemoglobin and urine were normal. The Mazzini was doubtful, Kolmer Wassermann was 4 plus, and the cardiolipin test was positive in 1:5 dilution. Vital capacity was 52 per cent of normal. Blood culture was negative; throat culture showed no pathogens; heterophil agglutination was negative, cold agglutinins negative, and trichinosis precipitin

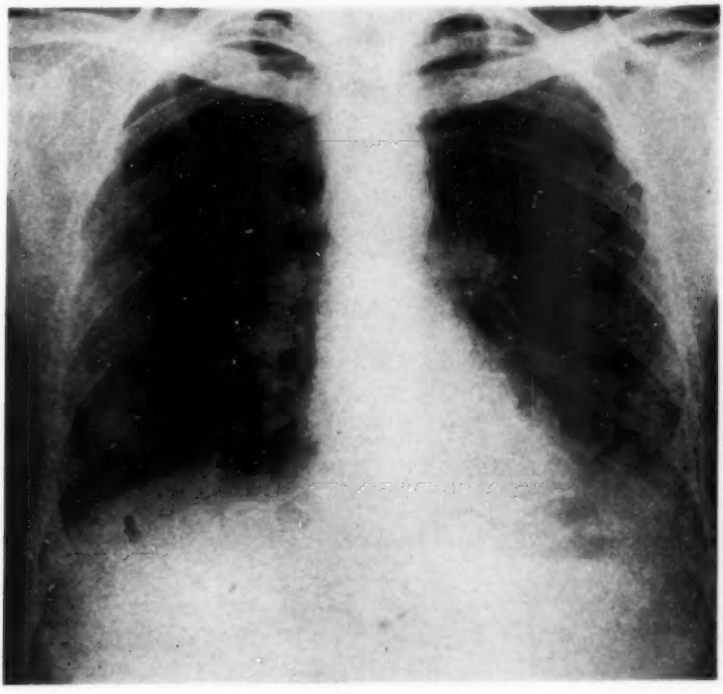


FIG. 2. Roentgenogram of November 24, 1950.

test was found to be positive in a dilution of 1:640. Chest x-ray showed a diffuse, mottled infiltration throughout both lungs, most marked in the lower lung fields, which was much more extensive than would be predicted from physical examination.

*Course in Hospital:* With the exception of tripelennamine hydrochloride given for urticaria, the patient received no specific treatment. His temperature fell to 38° C. by the second day, and remained at 38° C. until the fifth hospital day, when it became normal. On admission he was extremely uncomfortable, flushed and restless, but gradually improved over the next five days. On the third day he developed giant urticaria at the site of previous penicillin injections, and the next day showed an erythematous maculopapular eruption over the trunk, back and proximal extrem-

ities. Serial x-rays revealed increasing infiltration during the first four days, followed by gradual clearing, the lungs becoming entirely normal by the end of the second week. During the second to fourth days there was roentgen evidence of a small left pleural effusion. No chest pain, wheezing or productive cough was noted at any time. White count and differential changes are shown in the table. A sternal marrow aspiration on November 21 showed a total count of 138,000 per cu. mm., with 52 per cent eosinophils in all stages of development, with 3 per cent myeloblasts. Skin and muscle biopsy on the same date showed no abnormalities. By the end of the second week he appeared completely well. His vital capacity had returned to normal,



FIG. 3. Roentgenogram of November 27, 1950.

and his cold agglutinin titer remained normal. There were no changes in red count, hemoglobin or urine on repeated tests, and serum albumin and globulin remained normal. Follow-up serologic tests one month after admissions showed a positive Mazzini; Kolmer, 4 plus, cardiolipin test, positive in dilution of 1:5. Six months later, his cardiolipin test was positive in a dilution of 1:2. He demonstrated the highest degree of eosinophilia on the sixth hospital day—80 per cent eosinophils, with total white blood count of 42,900.

Intracutaneous tests were carried out on November 27 while the patient was showing decided eosinophilia but was otherwise well. A volume of .025 c.c. was used for each test, and the solution employed was crystalline sodium penicillin, Type G,

which had been diluted in 10-fold steps from a supply containing 1 million units per cubic centimeter. The 2,000-unit preparation provoked a small wheal and flare response within 20 minutes, whereas the 20,000-unit test provided a 2 plus or moderate reaction. When the patient was retested 16 days later with a new set of dilutions from the same supply, no response could be evoked by either of these strengths. However, when the original penicillin solution containing 1 million units was used, a response read as moderate to marked was elicited. The patient gave no response to control tests with saline diluent on either occasion. One could conclude from these limited tests that the patient's cutaneous sensitivity was of a transitory nature.

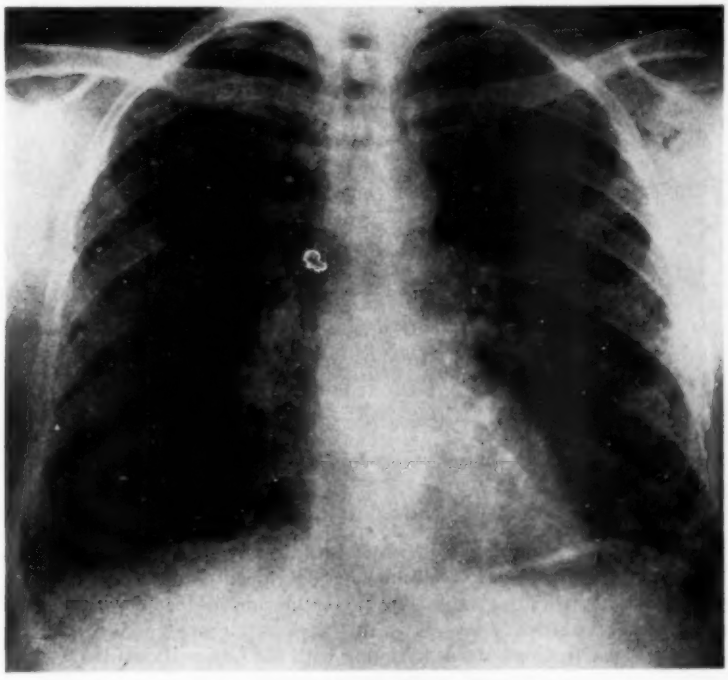


FIG. 4. Roentgenogram of November 28, 1950.

Although intracutaneous tests were also carried out on November 27 with procaine penicillin in strengths of 2,600 and 26,000 units per cubic centimeter, there was no response. This was no doubt due to the restraining vascular influence of the procaine.

On December 13, scratch tests were also done with the vehicle * used in the therapeutic preparation which had originally been given this patient (Cutter's Hypercillin). This vehicle consisted of sesame oil admixed with 2 per cent of aluminum monostearate. No wheal and flare reaction resulted. This negative result may have been referable to normergy, to the known insensitivity of the scratch test, or to a transitory sensitivity which had disappeared, as in the case of penicillin.

* Kindly supplied by Cutter Laboratories.

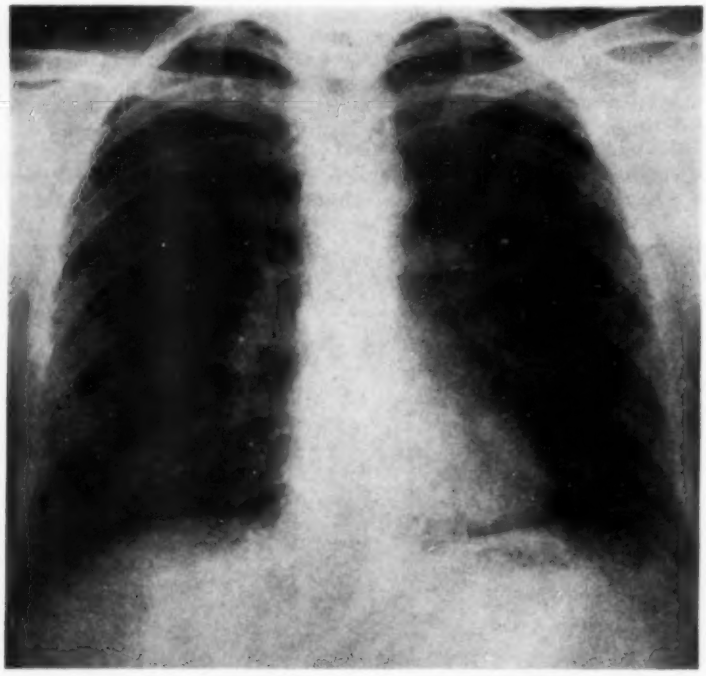


FIG. 5. Roentgenogram of December 4, 1950.

## DISCUSSION

This patient demonstrated a serum sickness type of reaction manifested by fever and urticaria. In addition, he developed patchy areas of pulmonary consolidation. Tripelennamine hydrochloride did not prevent the occurrence of the pulmonary lesions in this patient, although it did diminish the urticaria. These findings are in harmony with the observations of Dammin and Bukantz [1] on the control of experimental serum sickness by antihistamines. Similar reactions have been described by Falk and Newcomer [2] in two patients treated for secondary syphilis with penicillin in oil and beeswax. In the first case, local soreness occurred following the third injection. Chills and fever as well as evidence of thrombophlebitis followed the fifth treatment, and urticaria appeared at the site of the injection 11 days after institution of the injections. On the nineteenth day of the course of treatment, "decided accentuation of lung markings" was demonstrable on x-ray examination of the chest. This had disappeared entirely nine days later. In the second patient, headache, fever and cough were noted after the ninth injection, and a diffuse patchy infiltration which lasted some seven days was demonstrable by x-rays. In both these cases, as in the one presented here, there were few or no physical signs, and the peripheral eosinophilia reached its maximum as the lung lesions were definitely decreasing.

This phenomenon has been noted in other instances of Loeffler's syndrome of unknown etiology.[3] In the cases of Falk and Newcomer, skin testing failed to confirm the assumption that penicillin was the excitant, but it is well known that many cases of penicillin sensitivity fail to show cutaneous reactivity.[4] Harkavy described a similar situation in an asthmatic woman who developed migratory pulmonary infiltrations associated with arthritis, fever and renal changes following penicillin treatment. Muscle biopsy in this patient revealed arteritis.[5]

That this type of reaction is rare is shown by the fact that no instance could be found among 10,420 penicillin-treated patients surveyed by Anderson and Keefer in 1945.[6] Furthermore, no instance was noted in a review of 360 papers describing reactions to penicillin.[7] Other allergic responses described in the literature include urticaria, angioneurotic edema,[4, 6, 7] and occasionally anaphylactic shock,[8] myocarditis and hepatitis.[9]

It is widely believed that Loeffler's syndrome is a manifestation of antigen-antibody reaction in pulmonary tissues.[10, 11, 12] In cases that have come to autopsy,[10, 11, 12, 13, 14] the changes noted in blood vessels and in collagen have been suggestive of those produced by experimental sensitization.[15, 16] Furthermore, the tendency for Loeffler's syndrome to occur more frequently in patients with asthma is suggestive of an allergic basis for these lesions. Loeffler's syndrome in association with erythema multiforme has also been observed.[17] Bergstrand [11] postulated a basic similarity between Loeffler's syndrome, rheumatic fever and polyarteritis nodosa. Von Meyenburg [10] has suggested that the portal of entry of the allergen will determine the localization of the lesion in either peribronchial tissues (inhalation) or in periarterial tissues (blood-borne). It is interesting that in the single reported case of tropical eosinophilia with autopsy findings [14] the lesions were peribronchial and not perivascular.

In most cases, no obvious allergen can be implicated. In others, however, a variety of antigenic substances has been suspected. Among these are plant pollens [18] and bacteria such as the tubercle bacillus,[19] diplococcus,[10] brucella [20] and respiratory tract bacteria.[12] Parasites such as ascaris, trichina, cutaneous helminths, *Endamoeba histolytica* and *Fasciola hepatica* [3] have been associated with the syndrome.

It is possible that the syndrome follows a variable course, dependent upon the reactivity of the host and the nature of the allergen.

## Summary

A report is made of a case of Loeffler's pneumonia which developed subsequent to a course of penicillin therapy. That penicillin may have been the etiologic agent is suggested by the clinical course and the results of the skin testing.

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## BERYLLIUM GRANULOMATOSIS: REPORT OF A CASE SHOWING RESPONSE TO CORTISONE*

By Jacob John Robbins, Commander (MC) USN, *Chelsea, Massachusetts,* and William F. Lyons, Commander (MC) USN, *Jacksonville, Florida*

Beryllium poisoning is an industrial hazard which has appeared in the United States during the past 10 years. Beryllium compounds are commonly found in fluorescent lamps, radio, electronic and x-ray tubes, alloys and non-spark tools.[1] The metal is lighter (specific gravity, 1.85) than aluminum (specific gravity, 2.70).[4] Soluble dusts and fumes produce acute pneumonia and dermatitis. Insoluble dust in the lungs causes a slow development of granulomatosis.[2] The fibrosis of the lungs may develop over a period of years.[5] Particles embedded in the tissue require surgical excision for cure.[3] No suitable treatment was found before cortisone or ACTH. It is too early to evaluate the curative value of cortisone, but it has seemed life saving on two occasions in this case.

* Received for publication June 2, 1952.

## Case Report

The patient was exposed to beryllium in 1943 at the age of 19 at a beryllium factory in Ohio. She had been working in the barrel room in the basement for three weeks when she developed a cough, chest pain and headaches. On the basis of findings on roentgen examination of the chest she was hospitalized for three months at a sanatorium under observation for tuberculosis. At the end of this time she returned to work at the same factory for about one year, being employed as an inspector of beryllium powder and bricks. She has had no employment involving dust fumes or radiation material since that time.

She was first seen at the U. S. Naval Hospital, Jacksonville, Florida, in September, 1949, when she was given prenatal care and delivered of her second child. As in her first pregnancy, she complained of dyspnea during the last trimester but delivery



Fig. 1.



Fig. 2.

was uneventful. Roentgen examination at that time revealed infiltration of both lung fields.

The patient was first seen by the authors in February, 1951, when she reported to the medical clinic complaining of increasing dyspnea for the previous three months, chest pain and persistent cough. She stated that in the period from 1943 she had progressively lost 120 pounds—from 210 (figure 1) to weight at that time of 89 pounds (figure 2—photograph taken in November, 1951, after 25 pound weight gain).

Physical examination at that time revealed an emaciated, chronically ill young woman in severe dyspnea, coughing constantly and obviously in severe distress. Shortness of breath was so severe that she could barely walk the distance of 20 feet from the waiting room to the examining room. Moist and sibilant râles were audible throughout both lung fields. Chest roentgen examination (figure 3) showed massive infiltration of both lungs, with considerable increase in intensity since the film taken in 1949.

Sputum studies failed to reveal acid-fast bacilli. Electrocardiogram (figure 4) showed evidence of right ventricular hypertrophy. Vital capacity was less than 300 c.c. She was given courses of treatment with terramycin and aureomycin in the hope of obtaining clinical improvement by combating possible secondary infection, but no effect was evident. She required continuous oxygen therapy and large doses of codeine throughout her hospital stay. On the basis of personal communication from Dr. Harriet Hardy, of the Massachusetts Institute of Technology, she was again



FIG. 3.

hospitalized and a trial course of cortisone was begun. By the third day of treatment, when a dosage of 200 mg. daily was first reached, dramatic improvement was noted. By the fifth day cough and dyspnea had almost completely disappeared, and oxygen and sedation could be discontinued. Temperature, which had been spiking to 101° F., returned to normal. Vital capacity had risen from 300 c.c. to 1,000 c.c., and patient could be out of bed and care for herself without difficulty. Her appetite and feeling of general well being improved so that at time of discharge she had gained eight pounds of weight. The dosage of cortisone was gradually reduced (without return

of symptoms) to 50 mg. every other day for a period of four weeks. At this time the supply of cortisone was temporarily exhausted. One week after the last injection she again had to be hospitalized, with the identical symptoms she had had on first admission. Cortisone, then again available, was begun on the same schedule and dramatic response was again obtained. Since that time she has been maintained on 25 mg. cortisone by mouth daily. She has gained to her present weight of 117 pounds and is able to do most of her housework without excessive dyspnea. It is noted that her symptoms tend to recur just before her menstrual period, and additional amounts of cortisone are required at these times to control her symptoms. Chest roentgen findings have, however, shown no significant change. At various times she has exhibited serious psychiatric disturbances, marked by depression with suicidal ten-

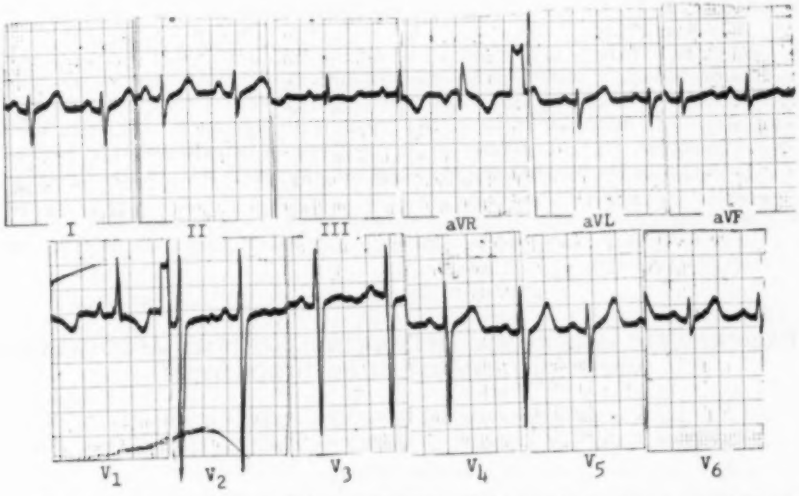



FIG. 4. Electrocardiogram, February 15, 1951. Right ventricular hypertrophy indicated by (1) right axis deviation, (2) sagging S-T segments, (3) deep S waves over left precordium.

dencies. Under psychiatric treatment, and since settlement of her industrial compensation claim, she appears to have made a good adjustment in recent months. It was felt for a time that the hormonal therapy may have accentuated her psychiatric difficulties, but since her respiratory symptoms were so aggravated when dosage was reduced below 25 mg. daily, this schedule has been maintained for more than 12 months without untoward effects.

## SUMMARY

1. A case is reported of beryllium granulomatosis in which severe respiratory symptoms did not develop until eight years following exposure.

2. Treatment with cortisone resulted in dramatic symptomatic improvement, although findings on chest roentgen examinations were not materially affected.

3. This response has been maintained for a period of 18 months on daily dosage of 25 mg. cortisone by mouth, without significant untoward reactions.

4. Review of the literature reveals three reports [6, 7, 8] on a total of seven cases of beryllium granulomatosis which have responded to ACTH, but none in which cortisone was effective.

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## PANCREATIC ADENOMA (HYPERINSULINISM) ASSOCIATED WITH NEUROMUSCULAR DISORDERS *

By RALPH W. BARRIS, M.D., Ph.D., *LaJolla, California*

### INTRODUCTION

THE neuromuscular disorders belong to a clinical group in which the cardinal signs and symptoms are related to a progressive wasting of muscles. As a group, these disorders are etiologically vague and pathogenically unspecific. In the broader classification of neuromuscular disorders, there are included those states characterized by some demonstrable alteration in the anterior horn cells, or in their peripheral processes, or by some alteration in structure in the muscle fibers, per se. The designation "progressive muscular atrophy," or the alternative designation "progressive spinal (or nuclear) muscular atrophy," is usually employed to designate that group of muscle wasting states in which the anterior horn cells are the site of demonstrable alteration (amyotrophy). In progressive muscular atrophy we see, therefore, the progressive wasting of muscles, muscle fasciculations, increased myotatic irritability, electromyographic (E.M.G.) evidence of fibrillation, and a progressive motor weakness involving chiefly the trunkal and appendicular muscles. In the most classic form of this disorder there is an inevitable progression of the wasting of muscles, to the point of almost complete motor disability of the patient, with an ultimate bedridden status, and death.

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Our knowledge of this disorder, as well as of other progressive muscle wasting states, is of course meager, so that every clue as to etiology or pathogenesis seems worthy of pursuit. No clue has as yet been obtained, for example, as to the character of any presumptive toxic, viral, chemical, genetic, metabolic or deficiency factors which might in such cases be responsible. Until recently, the rôle of the endocrines in etiology and pathogenesis has not been emphasized nor supported by clinical evidence. However, the implication of a disordered endocrine function in progressive muscle wasting states has become more and more impressive, as more and more clinical observations have been recorded.[1-6]

There seems sufficient reason, therefore, for reporting here in brief the study of a case of progressive muscle wasting in which an endocrine factor seemed responsible. In this instance, there was observed a generalized progressive wasting of muscle, muscle fasciculations, E.M.G. evidence of muscle fibrillation, increased myotatic irritability and progressive motor disability. Of greater importance, perhaps, is the observation that this presumably inexorable progression of muscle atrophy was arrested following the discovery and surgical removal of a tumor of the pancreas, histologically confirmed as an islet cell adenoma.

Interest is also added to these observations by a search of the literature, which reveals that this is the fifth such case to be reported, all since 1946; furthermore, in four of these cases removal of a pancreatic adenoma brought about an arrest of the signs relating to progressive wasting of muscles; in the fifth case, in which a pancreatic adenoma was not discovered until autopsy, there was microscopic evidence of an associated severe and widespread degeneration of anterior horn cells of the spinal cord (amyotrophy).

## Review Of Literature

Silfverskiöld in 1946 [5] reported his observations on two male patients, ages 17 and 34, in whom he noted a progressive generalized wasting of muscles, muscle fasciculations, E.M.G. evidence of fibrillation, increased myotatic irritability and a progressive motor disability, associated with the existence of a pancreatic adenoma, the progression of clinical signs being arrested by surgical removal of the tumor, histologically verified as an islet cell type of adenoma.

A third case, that of a male, age 23, was reported by Lidz et al.[2] in 1949. In this case, as in the above two cases, a pancreatic islet cell tumor was discovered and removed surgically, with an arrest in the signs and symptoms of progressive wasting of muscles, muscle fasciculations, increased myotatic irritability and progressive motor disability. There were no sensory abnormalities noted and no other neurologic abnormalities.

A fourth case, that of a female, age 33, has recently (1951) been reported by Tom and Richardson.[7] This case is notable not only because progressive generalized muscle wasting was present, but also because at post mortem not only was an islet cell tumor found but severe and widespread degeneration of the ventral horn cells of the spinal cord was demonstrated histologically.

## Case Report

A 42 year old white male salesman was first seen on November 8, 1950, with the complaints of a progressive weakness and wasting of his muscles, and a subjective awareness of a "quivering" feeling in his muscles, for approximately one month.

During the preceding week he had noted especial difficulty in climbing stairs, walking for any distance, buttoning his shirt, holding a pencil, using his knife and fork and, in the previous few days, had begun to note that his feet would tend to "slap" after walking any distance.

Further inquiry revealed that for the previous year he had been noting increasingly frequent transient attacks of weakness, associated with tremulousness, mild

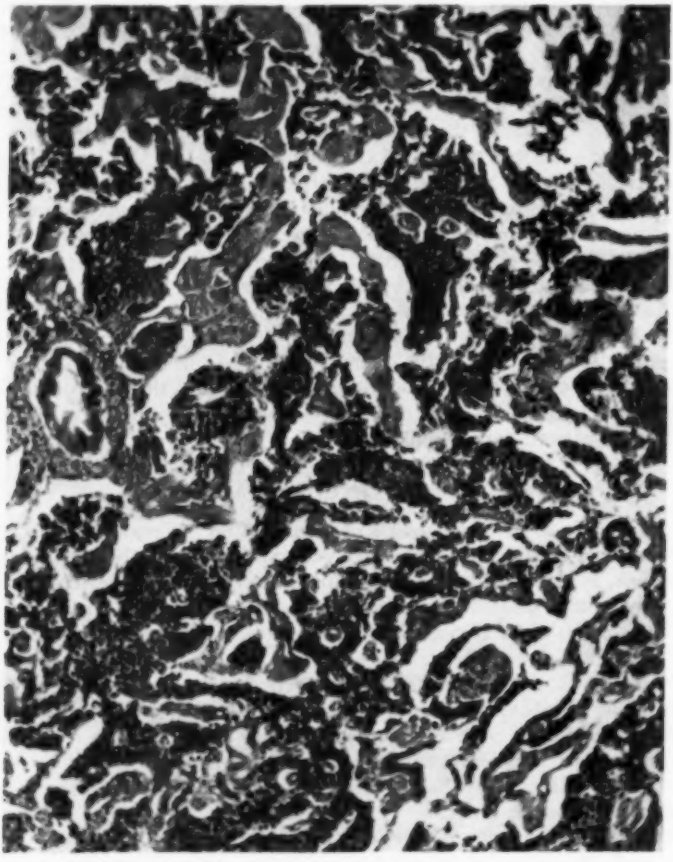


FIG. 1. Pancreatic islet cell adenoma (low power).

disorientation and confusion, and "blurring" of vision and diplopia, and that these tended to occur more often on awakening in the morning, or just before breakfast. It had been discovered that eating brought these attacks to a rapid resolution. Sweetened orange juice was eventually used for their amelioration. Several months after the onset of these attacks he consulted a physician who made a diagnosis of hyperinsulinism, repeated blood sugar levels being subnormal (30 to 40 mg.). An exploratory laparotomy failed to establish the existence of a suspected pancreatic

adenoma, but approximately two-thirds of the tail of the pancreas was resected. His early morning attacks continued, however, and within one month he had noted the signs and symptoms of progressive muscle wasting.

At the time of his examination, approximately one month later, there were noted a diffuse atrophy of moderate degree of the appendicular and trunkal musculature, generalized muscle fasciculation, increased myotatic irritability and E. M. G. evidence

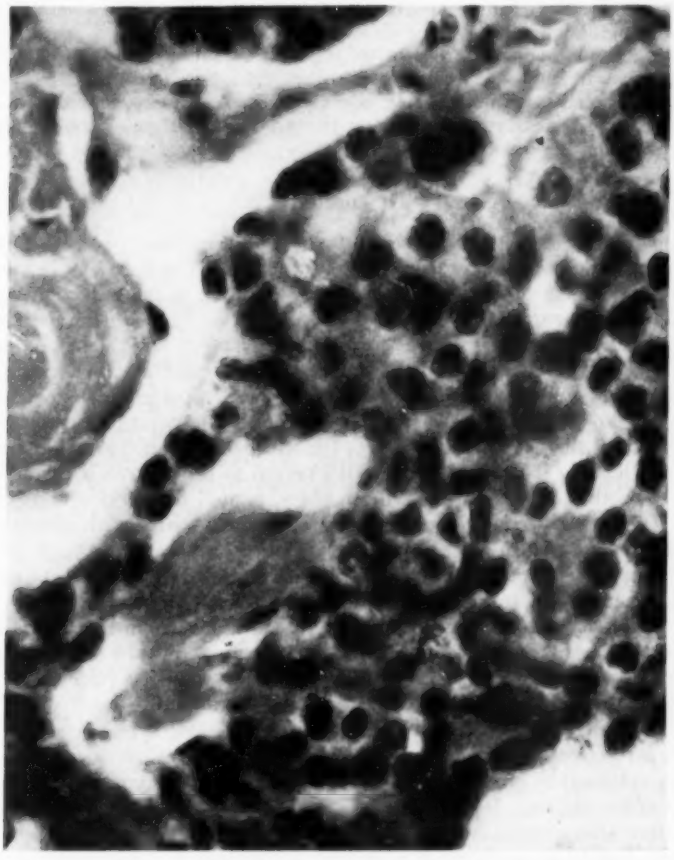


FIG. 2. Pancreatic islet cell adenoma (high power).

of fibrillation. Walking was difficult and of the "steppage" type; hand grasps were weak; rising to a sitting or standing position was difficult. All deep reflexes were intact and hyperactive except the Achilles reflexes, which were diminished. No sensory abnormalities were noted. All other neurologic findings were within normal limits.

He continued during the next few weeks to have transient early morning attacks associated with hypoglycemia, blood sugar levels being reported as subnormal (6 mg.,

15 mg. and 18 mg. per cent on three successive occasions). Muscle wasting and muscle fasciculation continued, with increasing motor disability. Surgical consultants concurred in a diagnosis of hyperinsulinism and recommended reëxploration for possible pancreatic adenoma. On February 1, 1951, four months after the onset of progressive muscle wasting, a pancreatic adenoma measuring 2 cm. in diameter was removed from the inferoposterior surface of the head of the pancreas and histologically verified as an islet cell tumor (figures 1 and 2).

No further early morning attacks or associated hypoglycemia were noted, and muscle wasting and motor disability were arrested. In the course of several weeks, with the aid of physiotherapy, the patient regained considerable motor capacity and the ability to walk for increasingly longer distances. Seven months after removal of the pancreatic adenoma he was able to grasp a pencil, to write, to button his shirt and to walk approximately a mile without tiring. He had regained nine pounds of the weight lost during his illness.

## Discussion

The pathogenesis of the clinical entity commonly referred to as "progressive muscular atrophy" remains obscure. Duchenne (1848) and Aran (1850) were the first to give their views as to pathogenesis, affirming its muscular (myogenic) as opposed to its neural (neurogenic) origin. In 1853 Cruveilhier reported that in such cases he had noted a slimness of the anterior roots, and thus attention was focused on the neurogenic origin of progressive muscular atrophy. This view was later given full support by Luys, who in 1860 reported that degenerative changes could be observed in the anterior horns of the spinal cords at postmortem study. Within the next decade or two, the work of Leyden (1876), Landouzy (1885), Déjérine (1885) and Erb (1891) served to bring about a clear distinction between the progressive muscle atrophies, related to anterior horn cell alteration (neurogenic), and the muscle dystrophies, associated with alterations in the muscle fibers per se (i.e., myogenic). Since that time, although anterior horn cell alteration is a sine qua non of progressive muscular atrophy, the etiology and pathogenesis of anterior horn cell dissolution remain obscure.

We have felt it appropriate, therefore, to call attention in this paper to the possible rôle of a disordered endocrine function in cases clinically characterized by progressive wasting of muscles, muscle fasciculations, E.M.G. evidence of fibrillation, increased myotatic irritability and progressive motor disability.

The clinical features of all of the five cases reviewed herein were identical. All were associated with the existence of a pancreatic islet cell tumor. Four cases were characterized by an arrest in the progress of signs and symptoms on surgical removal of the tumor. In the fifth case,[7] which came to autopsy, not only did postmortem study reveal a pancreatic adenoma but also, and more important, there was histologic evidence of a severe and widespread degeneration of anterior horn cells of the spinal cord.

No clearer evidence could be offered to support the hypothesis that, at least in some cases conforming to the clinical entity of progressive muscular atrophy, an abnormal endocrine function may bring about the sine qua non of this disorder, anterior horn cell dissolution (amyotrophy).

It might be questioned whether, by this evidence, we should be led to believe that pancreatic adenomata are usually responsible for the signs and symptoms seen in progressive muscular atrophy. Such a conclusion seems to be far from

warranted. What does seem important is that, either in the islet cells or in some remote endocrine gland (anterior pituitary, thyroid, adrenals), sufficient hormonal imbalance or altered hormonal function exists to be responsible for ultimate anterior horn cell dissolution. The well known hormonal antagonisms which exist between the islet cell hormone, or hormones, and those of the anterior pituitary,[1] and the physiologic interdependence of these and other hormone-producing organs, need no emphasis. In the five cases reviewed here there can be little doubt of an endocrine pathogenesis, these cases clinically conforming, except for their arrest by removal of an islet cell tumor, to the clinical designation of "progressive muscular atrophy." Whether hormonal factors are responsible for all such cases —whether pituitary-islet cell, pituitary-adrenal-gonadal or pituitary-thyroidal or other endocrine system dysfunctioning is in whole or part of etiologic significance in progressive muscle wasting states (amyotrophy) needs further study.

## Summary and Conclusions

1. Five cases, one an original case, have been described in which progressive generalized muscle wasting, muscle fasciculations, increased myotatic irritability and progressive motor disability were in evidence.

2. In all of these cases a pancreatic islet cell adenoma was discovered; four were surgically removed, and one was removed post mortem.

3. An arrest of the above signs and symptoms followed upon surgical removal of the islet cell adenoma.

4. In one of these, coming to post mortem, histologic evidence of widespread and severe degeneration was found in the anterior horn cells of the spinal cord.

5. Emphasis is given the probable rôle of endocrine dysfunction in the genesis of progressive muscular atrophy.

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# SENSORY NEUROPATHY ASSOCIATED WITH CARCINOMA OF THE ESOPHAGUS: REPORT OF A CASE*

By M. C. H. Dodgson, M.D., *Bristol, England,* and H. L. Hoffman, M.D., F.R.C.P., *Bath, England*

Although it is well recognized that degenerations in the peripheral and central nervous systems may accompany carcinoma in the absence of malignant metastases,[1-6] no further histologically proved cases of sensory neuropathy have been reported since those of Denny Brown, both of which occurred with carcinoma of a bronchus. In these he described a primary degeneration of the cells of the dorsal root ganglia, with degeneration of the dorsal columns of the spinal cord, dorsal nerve roots and of a large proportion of fibers of those peripheral nerves which were examined. In addition, there was an apparent primary degeneration of the voluntary muscles. A third case of sensory neuropathy is recorded below, occurring in association with carcinoma arising at the upper end of the esophagus.

## Case Report

A 54 year old male complained of discomfort in the throat and hoarseness dating from July, 1949; as the result of subsequent investigations, including biopsy in April, 1950, a diagnosis of carcinoma in the region of the left pyriform fossa was made.

Previously, amputation of the right leg had been performed in 1902 for osteomyelitis, which had also affected the left arm, leaving it wasted and weak. At about the time of the biopsy, i.e., about six months before death, weakness and tingling in the left leg and tingling in both hands were first noticed. At this time there were noted peripheral loss of sense of light touch in the limbs, incoördination and loss of position sense in the right arm and left leg, and absent tendon reflexes in the leg. The findings in the cerebrospinal fluid were: lymphocytes, 2 per cubic millimeter; albumin, 45 mg. per cent; slight excess of globulin; Lange, 0112210000; Wassermann reaction, negative.

Radiotherapy to the tumor was instituted, and over a period of six weeks a total dose of 2,000 r. was given, simultaneously with vitamin therapy.

Details of the latter are as follows: Given intramuscularly, daily for the first week and subsequently on alternate days: thiamine, 50 mg.; riboflavin, 4 mg.; nicotinamide, 200 mg.; pyridoxine HCl, 5 mg. Given by mouth: synthetic vitamin E (Roche), 100 mg. thrice daily, and pantothenic acid, 50 mg. twice daily.

On examination during the first week of treatment there was found to be hyperesthesia, but diminished sensation to light touch in the area supplied by the first division of the left trigeminal nerve. Peripheral sensory loss to light touch, pinprick and vibration was present in the limbs, although position sense was now apparently normal. Three weeks later (May 5), wasting of the interosseous muscles of both hands was noted and fibrillation was seen in the muscle of the right hand and forearm. On July 14 paresthesias in the arms were still complained of, although they had diminished in the leg; swallowing of solids was now becoming difficult. At the last neurologic examination, on August 11, there were partial anesthesia of the left side of the face and wasting of the small muscles of the hands; tendon reflexes, however, were present in the arms and leg. There was, in addition, some generalized muscle

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wasting associated with cachexia. The patient died at his home on September 6, 1950.

At necropsy the cause of death was found to be bronchopneumonia. There was a partially necrotic tumor, histologically a poorly differentiated squamous cell carcinoma, arising from the left wall of the upper end of the esophagus and invading the larynx and the soft tissues of the neck, with metastases in neighboring lymph glands (figure 1).

In the spinal cord there was evidence of recent bilateral symmetrical degeneration of both posterior columns throughout the whole of their length (figure 2), with the persistence in the tissue of myelin fragments, neutral fat and nonstaining, doubly refractile crystals. Many axis cylinders in these tracts had disappeared and others were fragmented, while a minority were preserved, although thickened in many instances (figure 3). There was a gliomesodermal reaction which was strictly confined to the posterior columns and posterior horn gray matter, astrocytic and microglial proliferation occurring with small perivascular collections of lymphocytes and macrophages. The blood vessels in the meninges covering the posterior columns showed similar perivascular inflammatory cellular exudates. Apart from this there was no meningeal reaction, nor was there any evidence of neoplastic involvement.

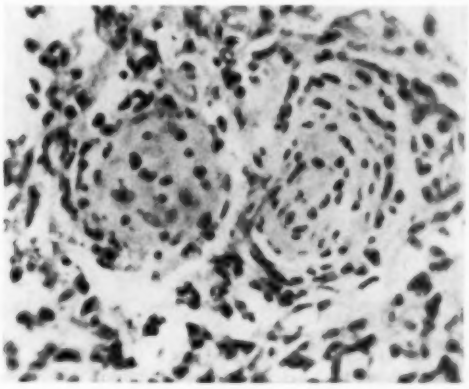


FIG. 1. Esophageal tumor, showing two cell nests.

The anterior horn cells showed marked atrophy of all cell groups at levels C 6 and C 8, more conspicuously on the left side than on the right, although this loss was not so obvious at C 4 and at higher levels. In the midthoracic region all anterior groups were involved to some extent; however, the lateral column cells were not apparently affected, although Clarke's column could not be identified on either side. At L 3–4 there was evident sparsity of cells in the anteromedian and particularly in the posterolateral groups on the side of the amputation, whereas on the left the loss of cells in these groups was not obvious. Again, in the sacral cord it was evident that there had been considerable loss of anterior horn cells in all groups on the amputated side, although obvious cell depletion on the opposite side was apparently confined to the anterolateral group.

It is unfortunate that the posterior root ganglia were not available. In a single fragment found attached to the right seventh cervical posterior root many of the ganglion cells appeared to be undamaged, although a few had evidently succumbed and were undergoing neuronophagia (figure 4). There was also an apparent in-

crease in the density of distribution of the interstitial cells. No evidence of neoplastic invasion was seen in serial sections.

Changes in the peripheral nerves were inconspicuous. Although axis cylinders were present in the posterior roots, they showed considerable beading, and there was a noticeable pallor in the staining of myelin in the posterior roots as compared with more normal appearances in the anterior roots. There was no evidence of active myelin breakdown, of the presence of neutral fat, or of an inflammatory reaction in the peripheral nerve, although axis cylinders appeared to be rather thinly distributed. Muscle fibers in the tongue and pretracheal muscles showed varying degrees of atrophy, with in some instances loss of transverse striations, although there was no myositis. Muscle nerve endings could not be clearly demonstrated.

The Purkinje and granule cell layers of the cerebellum were normal, as were the dentate and inferior olivary nuclei and cornu ammonis. The lower half of the pons and the medulla were missing from the specimen, and it was therefore not possible to examine the posterior column nuclei or the connections of the trigeminal nerves. The motor nuclei of cranial nerves in the midbrain and upper part of the pons were normal and showed no pellagrous changes, nor was there any evidence of Wernicke's encephalopathy. No pathologic changes were detected in the basal ganglia, central



FIG. 2. Posterior column degeneration in cervical cord.

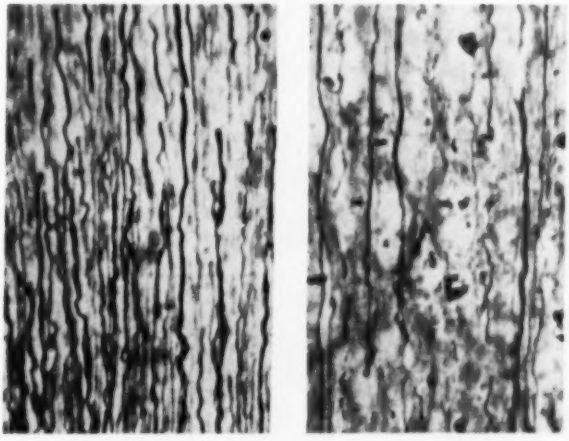
cerebral white matter or cerebral cortex, although there was a characteristic nerve cell change in the main sensory nucleus of the thalamus on either side which was thought to be an example of transneuronal degeneration.

## DISCUSSION

The clinical features and histologic changes in the cord so closely resemble those described in Denny-Brown's two cases of sensory neuropathy as to satisfy us that we are dealing here with an example of the same condition, despite the less conspicuous involvement of the peripheral nervous system in our case. Although Denny-Brown interpreted the changes in the posterior columns as indicating Wallerian degeneration following the loss of posterior root ganglion cells, the alternative possibility—that these changes occur primarily as a posterior column degeneration—cannot be ignored. Since our present pathologic material is incomplete in this respect, the investigation of further cases in which the posterior root ganglia have been removed post mortem would seem to be particularly desirable in order to settle this point. With regard to the histologic diagnosis of the condition, it must be remembered that sensory and motor disturbances in

cases of carcinoma may result from microscopic infiltration of the nerve roots by tumor, as in a case reported by Guichard and Vignon,[7] and care must be taken to exclude this possibility.

Although predominantly so, this condition is evidently not purely a sensory degeneration, since there is some involvement of the motor system as well. Denny-Brown's cases showed evidence of muscular atrophy, thought to be greater than would be accounted for by the general cachexia, confined to the thigh muscles in his case 1, but more generalized in case 2. Histologically, both showed considerable atrophy of thigh muscles associated with an axonal reaction in some of the anterior horn cells, although there were no striking changes in muscle nerve endings. Clinical evidence of muscle wasting was definite, also in our case. Allowing for long standing absence of anterior horn cells in the cervical



(*a*) (*b*)

FIG. 3. (*a*) Normal axones in lateral column. (*b*) Axonal degeneration in posterior column.

region related to an old osteomyelitis of the left arm, and in the lumbar and sacral regions as a sequel of the leg amputation, the histologic evidence suggested that the sensory changes had been accompanied also by a recent loss of anterior horn cells, particularly in the cervical cord.

Up to the present time two histologically proved cases of carcinomatous sensory neuropathy have been recorded. In both of these, and in the other cases of pure spinal neuropathy reported by Wyburn-Mason and Lennox and Prichard, the growth was invariably in the bronchus. The case described here suggests that a similar neuropathy may be associated with carcinoma in other sites. With regard to this point the paper of Brain, Daniel and Greenfield, already mentioned, is of interest. In this they discuss the relation of carcinoma to subacute cortical cerebellar atrophy. Carcinoma was present in 11 of 16 cases, and in six of these degeneration of the spinal tracts had also occurred, e.g., dorsal columns, spino-

cerebellar or pyramidal tracts. The site of carcinoma was bronchus in three cases, ovary in two and breast in one.

The mode of production of sensory neuropathy is still unknown. Denny-Brown has pointed out the similarity of the clinical picture to that of "nutritional ataxia," a condition, unassociated with carcinoma, which has been encountered in prisoners-of-war existing for long periods on a meager cereal diet. He also noted histologic resemblances in his cases to changes which had been induced in animals fed on diets deficient in pantothenic acid and vitamin E.[8-11] Kluver and Weil [12] report a further example of a specific degenerative change in the central

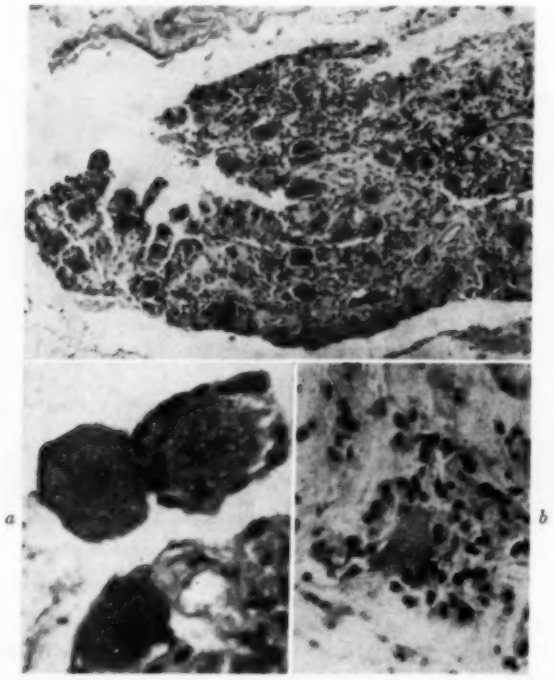



FIG. 4. *Above:* Part of a cervical posterior root ganglion. *Below:* (*a*) Normal ganglion cells. (*b*) Damaged ganglion cell undergoing neuronophagia.

nervous system, in a rhesus monkey with carcinoma of the tongue; transmission of the tumor into the tongue of a second monkey resulted in the production of similar changes in the central nervous system. In both instances there were severe cell changes in the anterior horn cells throughout the brainstem and cord, although the posterior columns were unaffected. These workers believe that the responsible agent, possibly a virus, enters the central nervous system via lymphatic connections between the pharynx and the subarachnoid space. The available evidence seems to suggest that carcinomatous neuropathy arises as the result of a metabolic disorder, for the production of which the presence of a

carcinoma is responsible. Absence of more than a slight response to vitamin therapy, as in our case, is not in favor of an induced vitamin deficiency being the main etiologic factor, although one cannot be certain that, by the time such therapy has been instituted, irreversible changes have not already occurred in the central nervous system. The possibility that sensory and other neuropathies in association with malignant disease indicate the invasion of the nervous system by a virus should not be disregarded.

## Summary

A third histologically proved case of carcinomatous sensory neuropathy is described, associated with a squamous cell carcinoma of the upper end of the esophagus. The etiology of this and allied conditions is discussed.

### Acknowledgment

Material from this case was shown to the Neurological Section of the Royal Society of Medicine on March 6, 1952. We have pleasure in recording our thanks to the Hon. Editors of the Proceedings of the Society for their permission to publish the case in detail.

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# MIXED ADENOMA (HAMARTOMA) OF THE LIVER: REPORT OF A CASE *

By ROBERT M. LEVENSON, M.D., *San Francisco, California,* and DAVID G. MASON, M.D., *Seattle, Washington*

PRIMARY benign tumors of the liver, other than angiomas, are rare. Hoffman [1] reviewed the literature in 1942 and was able to find only 58 cases reported. He added one case of his own. No attempt was made to classify these lesions.

Primary benign liver tumors may arise from either the liver cells or the bile duct epithelium. These are classified as liver cell adenomas or bile duct adenomas. In addition, a third type of tumor occurs. This lesion is composed of both liver cells and bile ducts. Such lesions have been classified by Warvi [2] as

TABLE I

| Author | Age of Patient | Weight of Tumor | Gross Description | Microscopic Description |
|---|---|---|---|---|
| Patton[11] | 16.5 mo. | 1,575 gm. | In rt. lobe, roughly lobulated 8 cm. cyst containing yellow fluid. | Poorly formed liver cords and fibrous tissue. |
| Kay and Talbert[9] | (a) 7 mo. | 150 gm. | On caudate lobe, broad pedicle, roughly lobulated, nodular surface. | Cells in cords and nests with fibrous trabeculae. No bile canaliculi. (Resembles cirrhosis.) |
| | (b) 13 yrs. | — | Large nodular mass replacing left lobe and part of right lobe; not encapsulated. | Distorted lobular pattern. Central vein eccentric or absent. |
| Benson and Pemberthy[12] | 7 mo. | 60 gm. | Tumor at lateral margin of right lobe. Broad base. Surface vascular, smooth, resembling liver. | Irregular lobules of large liver cells; mod. fatty change; dense fibrous tissue and marked duct proliferation. |
| Branch, Tonning and Skinner[8] | 32 yrs. | — | Encapsulated 6 cm. mass resembling liver but paler and firmer. | Suggestive of cirrhosis with bile duct proliferation. |
| Hoffman[1] | 38 yrs. | — | 7.5 cm. roughly nodular mass projecting from the inferior border of the right lobe. | Suggestive of cirrhosis with hepatitis. |
| Franklin and Downing[10] | 23 yrs. | — | 20 by 10 by 10 cm. mass attached to right lobe by pedicle. | Irregular cords of cells; no lobular pattern; bile ducts present. |
| Ladd and Gross[5] | 8 mo. | 400 gm. | — | — |
| Gerding et al.[3] | 8 yrs. | — | 12 cm. nodular reddish tan mass deeply seated in the liver. | Irregular cords of large cells; bile ducts in fibrous tissue. |

mixed type adenomas and by others as hamartomas. Gerding [3] has recently proposed the imposing title of hamartomatous cholangiohepatoma.

We are reporting a case of a mixed type adenoma.

The term hamartoma was introduced by Albrecht [4] in 1904 to designate tumors composed of normal tissue elements occurring in abnormal proportions. Such unrelated diseases as tuberous sclerosis, syringomyelia, multiple neurofibromatosis and hemangiomas, as well as mixed adenomas of the liver, are included in the so-called hamartomatous diseases. Hamartomas appear to occupy an intermediate position between hyperplasia and neoplasia.[5] Some, however, do have

* Received for publication March 31, 1952.
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malignant potentialities, and the development of sarcomas from neurofibromas is not uncommon.

Since the term hamartoma includes such a wide group of lesions, we agree with Branch [6] that the term mixed adenoma is preferable for those lesions of the liver. Its hamartomatous nature can be made clear by adding the term hamartoma parenthetically. Mixed adenoma of the liver is a specific name and is descriptive of the pathology present. It fits into a simple standard classification, as proposed by Warvi.[7]

Mixed adenomas of the liver are tumor masses of variable size. They may be encapsulated or circumscribed and intimately related to normal liver parenchyma. Most cases reported have been solitary lesions. One case of multiple nodules of variable size was described by Weidman.[8]

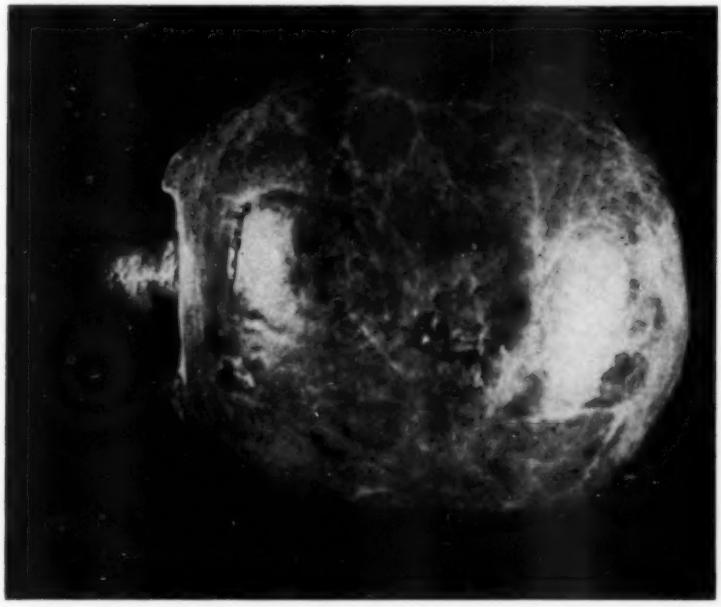


FIG. 1. Gross photograph of the tumor. Note normal liver on left.

Since 1942, nine cases which fit the classification of mixed adenoma of the liver have been reported. These have been summarized in table 1. Four of the patients have been less than one and one-half years of age, one was eight years, another 13 years, and three were adults from 23 to 38 years of age.

The symptoms referable to these tumors are chiefly pressure symptoms. The severity depends on the size and location of the mass. There may be vague right upper quadrant discomfort or pain. Some reports mention episodes of nausea and vomiting.[9]

Physically, the abdomen is prominent and a right upper quadrant mass can usually be palpated. It is generally quite firm and nontender. The surface may be either smooth or irregular.

All laboratory studies, including the usual liver function studies, have been within normal limits in the cases reported.

X-rays show variable degrees of displacement of the abdominal viscera downward and to the left. The case of Franklin and Downing [10] failed to concentrate dye in the gall-bladder on two occasions.

Because of the presence of an undiagnosed right upper quadrant mass, most of these patients are subjected to laparotomy. The preoperative diagnoses include liver tumor, mesenteric cyst, Gaucher's disease and von Gierke's glycogen storage disease. The healthy appearance of the patients makes a diagnosis of malignant disease unlikely.



FIG. 2. Cut section of tumor. Note normal liver on left.

In three of the cases reported the tumor was pedunculated and projected from the inferior surface of the liver. These were surgically removed without difficulty. One mass was encapsulated and three others were inseparable from surrounding liver.

Grossly, these lesions are usually nodular and resemble hyperplastic liver tissue. The surfaces are either smooth or lobular and, in most instances, quite vascular. On cut section the tissue resembles liver but is lighter in color and firmer. In Patton's [11] case and in the case being reported, a large cystic area was present in the central portion of the mass.

Microscopically, the liver cords are well formed, but the lobular pattern is absent. Apparent "central veins" are scattered throughout the tissue, but there are no normal portal triads. There is an increase in the amount of fibrous tis-

sue, and many hyperplastic bile ducts are scattered through this tissue. Lymphocytes are commonly present in the fibrous tissue.

The presence of lymphocytes and the distorted appearance of the liver strongly suggest portal cirrhosis. The possibility exists that mixed adenomas might actually represent local areas of hyperplasia. Dr. Dorothy Anderson, quoted by Kay and Talbert,[9] states that she has never seen a case of cirrhosis in an infant which did not involve the entire liver. Such experience as this, in addition to the remote possibility of liver injury in the cases reported, supports the contention that this is not simply a local hyperplasia. The liver tissue outside the tumor has been reported normal in the cases where it has been examined. In adults, the chance of local hyperplasia is greater than with infants. However, if hamartomas were regenerating liver nodules, a greater number should be anticipated in adults. It is considered that mixed adenomas probably arise from fetal rests.

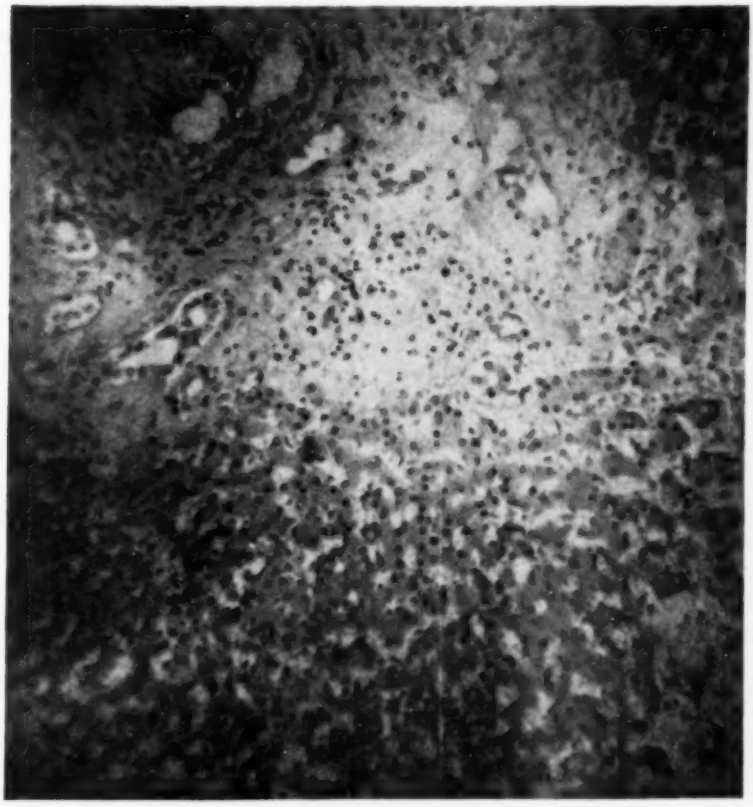


FIG. 3. Low power photomicrograph of the tumor. Note the hyperplastic bile ducts and the lymphocytes present.

## Case Report

A 15 month old white male child was admitted to the Providence Hospital on November 19, 1950, with the complaint of a distended abdomen. The abdomen had been large since birth and had become more prominent. There had been no other difficulties and the child had developed normally.

One month prior to admission a needle aspiration of a right upper quadrant mass had been performed. The specimen was not diagnostic, though it was mentioned that the cytoplasm of some of the cells looked foamy.

Physically, the child was well developed and well nourished. The abdomen was greatly distended and the superficial veins were prominent. A firm smooth mass occupied much of the right side of the abdomen. The lower edge of the mass was below the anterior superior spine of the ilium. Slight tenderness was noted on palpation.

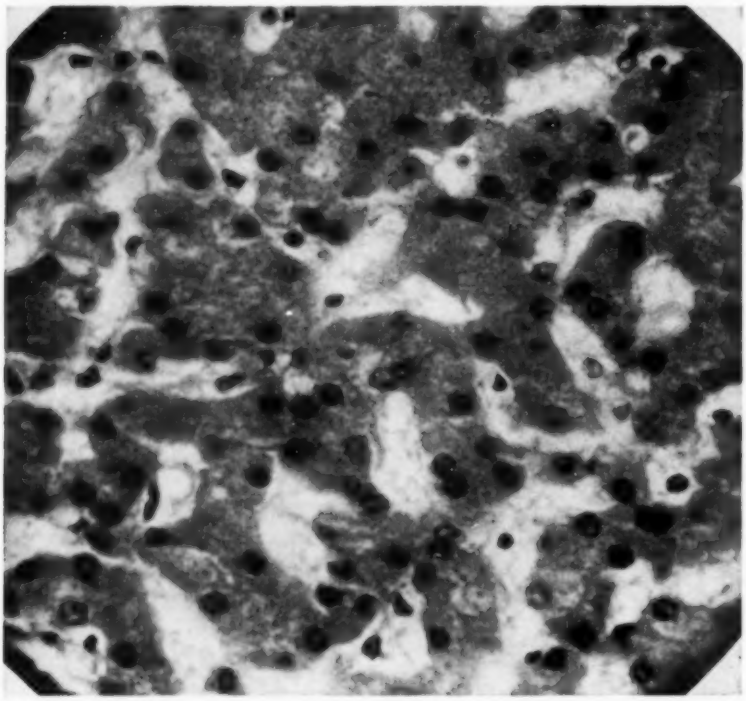


Fig. 4. High power photograph of the tumor. Note the normal appearance of the liver cells.

All laboratory studies were within normal limits.

On the day after admission the patient was taken to surgery, where a needle biopsy was attempted under general anesthesia. A satisfactory specimen could not be obtained. An exploratory laparotomy was then performed.

A large, smooth surfaced mass was present and involved most of the right lobe of the liver. The left lobe appeared normal. A thick fibrous capsule covered the free surface of the mass, and many dilated vessels were present beneath this capsule.

The biopsy needle had entered one of these vessels and there had been considerable bleeding from this source. Because the mass was deemed inoperable, a biopsy was taken and the abdomen closed. Postoperatively, the condition remained poor and the child died three days after surgery.

At autopsy, the only significant abnormality found was in the liver. It weighed 1,300 gm. Most of the right lobe was replaced by a mass covered by a thick fibrous capsule. Beneath this capsule were many distended veins. The left lobe and part of the right lobe distinct from the tumor posteriorly appeared to represent normal liver. The change on the anterior surface of the right lobe was limited by the falciform ligament. The tumor measured 14 by 10 by 10 cm. On section, the mass was composed of brown tissue slightly paler than the normal liver. Numerous punctate bile-stained areas were present. A cystic area 5 cm. in diameter and containing flocculent yellow material was present in the center of the mass. There was a distinct line of demarcation between the tumor and adjacent liver, but they could not be separated.

Microscopically, the liver cells appeared normal and the cords were well formed. No definite lobular pattern existed. Small veins were scattered throughout the tissue.

Numerous proliferating bile ducts were present at focal points. In these areas one noted occasional lymphocytes. There was no clear line of demarcation between tumor and normal tissue. The fibrous capsule was of moderate thickness over the free surface. Beneath the capsule there were prominent thin walled vessels and numerous proliferating bile ducts.

*Diagnosis:* Mixed adenoma (hamartoma) of the liver.

It is of interest that the biopsy taken at surgery was considered as an atypical cirrhosis prior to autopsy because of increased fibrous tissue, the proliferating bile ducts and the collections of lymphocytes.

## Summary

1. Nine cases of mixed adenoma (hamartoma) of the liver are reviewed.

2. A case of mixed adenoma of the liver occurring in a 15 month old child is reported.

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# EDITORIAL

## *THE NEWER ANTIHYPERTENSIVE DRUGS*

CONTROL of hypertension by any of the measures hitherto available has presented a baffling problem. Diets low in sodium or otherwise restricted, psychotherapy, sympathectomy, and the administration of many different drugs have all yielded good results in individual cases or groups of cases. Many cases, however, fail to respond or quickly become refractory. The recent discovery of drugs which are much more effective in maintaining a lowered blood pressure constitutes a major advance, and their current availability makes the problem of using them properly of immediate practical importance.

Hypertension is not a specific disease but rather a systemic reaction which may be induced by a variety of causes. In many cases a major factor is emotional tension which operates through the sympathetic system to cause vasoconstriction. Hypertension may also be caused by humoral pressor substances such as pherentasin, angiotonin, hypertensin, serotonin and perhaps norepinephrine. These substances in general do not operate through the sympathetics but appear to act more peripherally. Knowledge regarding these agents is still very incomplete, but there is evidence that they differ in their pharmacological properties and in their response to various antagonistic agents. In many cases of hypertension more than one etiologic agent presumably may be operative. It is not surprising, therefore, that no single satisfactory specific remedy for hypertension has been found.

"Neurogenic" hypertension should be relieved by interruption of the sympathetic pathways. That this is possible is indicated by the successful results obtained in a significant percentage of adequately extensive sympathectomies. The numerous failures, however, indicate that this is not a complete answer to the problem.

Similar results might be expected and can in fact be obtained by means of drugs which chemically block the sympathetic pathways. Of these, hexamethonium (Methium, Esomid, Hexameton, etc.) is the only preparation thus far carefully studied which has a sufficiently sustained action to offer promise as a therapeutic agent. This drug was first employed therapeutically by British investigators,[1, 2] who reported favorable clinical results. Hexamethonium, an anticholinergic drug, causes a blocking in the sympathetic and parasympathetic ganglia, interrupting both adrenergic and cholinergic impulses.[3, 4] It causes a dilatation of the peripheral vessels, in-

[1] Campbell, A., and Robertson, E.: Treatment of severe hypertension with hexamethonium bromide, Brit. M. J. **2**: 804, 1950.

[2] Restall, P. A., and Smirk, F. H.: The treatment of hypertension with hexamethonium, New Zealand M. J. **49**: 206, 1950.

[3] Fries, E. D., Finnerty, F. A., Jr., Schnapper, H. W., and Johnson, R. L.: The treatment of hypertension with hexamethonium, Circulation **5**: 20–27, 1952.

[4] Schroeder, H. A.: Control of hypertension by hexamethonium and 1-hydrazinophthalazine, A. M. A. Arch. Int. Med. **89**: 523–540, 1952.

cluding especially the renal vessels,[5] with a fall in blood pressure. It does not combat the effect of the humoral pressor substances, and it is reported (Fries et al.[6]) to augment the pressor effect of epinephrine and norepinephrine.

Hexamethonium is potent on intravenous injection, maximal effects being observed after 15 to 30 minutes, with a gradual but moderately rapid subsidence after one to two hours, usually to ineffective levels within four to at most six hours.[3] It may be administered orally, but absorption is poor (20 times the parenteral dose or more may be required), and variable and unpredictable, both in different subjects and in the same individual at different times. To maintain an effect, it must be given four to six times daily. There is a disturbing tendency in many subjects to develop a marked degree of tolerance rapidly, necessitating a progressive increase in dosage. Such large doses often cause distressing symptoms from the associated parasympathetic blockade, including dry mouth, cycloplegia, severe constipation and even ileus, urinary retention, transient impotence. These may sometimes be relieved by such parasympathetic stimulants as Urecholine.

There is marked individual variation in susceptibility to hexamethonium, especially to the initial dose,[3] occasional subjects reacting violently to relatively minute amounts. In practice it is difficult to avoid wide swings in blood pressure, the patient often partly escaping (unless dangerously large doses are given), or occasionally developing unexpected and sometimes alarmingly severe hypotensive reactions. It is now generally agreed that a more uniform lowering of blood pressure may be obtained in most cases if another type of antihypertensive drug is administered midway between the doses of hexamethonium. The most effective adjuvant now available is 1-hydrazinophthalazine (Apresoline).

1-hydrazinophthalazine differs in its action from hexamethonium and has been classed as a mildly adrenolytic and sympatholytic rather than a ganglionic blocking agent. The mechanism of its activity is not precisely known. According to Yonkman[7] it exerts a central action (midbrain or hypothalamus), inhibiting the emission of pressor impulses over the sympathetics. It inhibits the action of several humoral pressor substances, including pherentasin, serotonin and hypertensin.[8, 9] It reverses the action of epinephrine and partly inhibits norepinephrine. It causes a relaxation of the peripheral arteries and a fall in blood pressure with an increased cardiac output and increased blood flow in the coronary and particularly in the renal arteries.[8]

In large doses 1-hydrazinophthalazine will usually cause a profound fall in blood pressure, but in doses that are safe and tolerated, as the sole anti-

[5] Mills, L. C. et al.: Quoted by Schroeder.[4]

[6] Fries, E. D., et al.: Effect of "sympatholytic" drugs on cardiovascular responses to epinephrine and norepinephrine in man, Circulation 3: 254–259, 1951.

[7] Yonkman, F. F.: Quoted by Wilkinson et al.[8]

[8] Wilkinson, E. L., Backman, H., and Hecht, H. H.: Cardiovascular and renal adjustments to a hypotensive agent (1-hydrazinophthalazine: Ciba BA-5968: Apresoline), J. Clin. Investigation 31: 872–879, 1952.

[9] Schroeder, H. A.: The effect of 1-hydrazinophthalazine in hypertension, Circulation 5: 28–37, 1952.

hypertensive agent, it appears to be only moderately potent as compared with hexamethonium. It has rarely been possible to maintain normotensive levels with this drug alone.[9] In larger doses it is prone to cause severe headaches, often with nausea, vomiting, tachycardia, palpitation and prostration. This has been attributed to its action as an antihistaminase. These disturbances are usually less marked when it is given in conjunction with hexamethonium and may usually be controlled or moderated by Dramamine or other antihistaminics.

1-hydrazinophthalazine is well absorbed, and in practice oral administration is satisfactory. There is, however, a marked individual variation in susceptibility and a troublesome tendency to develop tolerance. According to Johnson et al.[10] troublesome tolerance to both drugs is less likely to develop if they are administered infrequently, two or at most three times a day. Schroeder,[4] however, reported that this can usually be overcome on a schedule of four to six doses a day by increasing the size of the dose, provided no dose is skipped. Interrupting the administration of either drug for a few days will temporarily restore sensitiveness to it. Abrupt interruption is dangerous, however, and withdrawal should be gradual, especially in malignant cases. Extreme care must be exercised on resuming the drugs to avoid the dangers of increased sensitivity.

The ultimate therapeutic value of these drugs will depend upon their effectiveness in maintaining a lowered blood pressure in doses which are not disabling and upon proof that such reduction is advantageous to the patient over the long term as well as regards the immediate effect. This evaluation is not yet available at this early stage in the use of these drugs. The technic of administration also must not be so cumbersome that it can not be continued indefinitely in ambulant cases, since there is no evidence that these drugs affect the underlying cause of the disease. The answers to these questions are still incomplete.

There is no doubt that these drugs can lower blood pressure. The problem is rather to secure a satisfactory reduction without precipitating dangerous hypotensive crises in which the pressure may fall to shock levels. By starting with small, usually ineffective doses, increasing them gradually to effective levels, observing the patients with great care, including many observations of the blood pressure daily, and readjusting the dose as indicated, it has been possible to accomplish this in large measure in a majority of the cases. The drugs are also useful for short periods to tide a patient over a period of hypertensive encephalopathy and to lessen the load in cases with left ventricular failure which have become refractory to the usual therapeutic procedures.

Schroeder [4] has reported a series of hospitalized cases treated with alternating doses of the two drugs. Of 20 patients with benign hypertension, normal levels were obtained in 14 and a significant reduction in four others

[10] Johnson, R. L., Fries, E. D., and Schnapper, H. W.: Clinical evaluation of 1-hydrazinophthalazine (C-5968) in hypertension with special reference to alternating treatment with hexamethonium, Circulation **5**: 833-841, 1952.

(with arteriosclerotic changes). After returning home, periods of disturbing hypotension necessitated some reduction of the dose and permitted partial escape, although still at reduced levels. Of 15 cases of malignant type, normal levels were obtained in only four, but a substantial reduction was obtained in nine others, and the malignant state was reversed in all 13. Two did badly. Subjectively patients who responded were usually relieved of the symptoms attributable to the hypertension, such as headache, palpitation, dyspnea, and often nervous tension and anxiety, although these drugs are not directly sedative. Objectively the manifestations of improvement resembled those seen after successful sympathectomy—relief of congestive failure, of the manifestations of hypertensive encephalopathy, of papilledema with absorption of hemorrhages and exudate, and a reversion to or toward normal of urinary abnormalities and elevated nonprotein nitrogen if renal function was only moderately impaired. Cases with severe renal disease showed no improvement in this respect although the blood pressure was sometimes lowered. Of 60 patients continuing treatment for 10 to 28 weeks, "30 have sustained normotensive levels." Essentially similar results have been reported by several other observers.[3, 8, 10, 11, 12]

These results were obtained, however, only in hospitalized patients who were under close supervision of observers experienced in the use of these drugs. Attempts to establish a suitable schedule of dosage in ambulant patients failed completely in about a third of the cases, and control at best was less complete because many patients can not or will not tolerate the disturbing side effects of the drugs while ambulant.

A practical limiting factor is the postural hypotension which in some degree seems inevitable if treatment is effective. If the supine blood pressure is brought quickly to normal levels, the further fall of pressure on standing may be completely incapacitating, particularly for an hour or two after administration of hexamethonium. Most subjects become more or less ad justed to this if treatment is continued, but syncopal attacks are common particularly if the subject stands quietly in one position. Apparently some elevation of the supine blood pressure must often be accepted to avoid incapacitating hypotension when erect. Fortunately patients may obtain significant improvement from such partial control.[4, 11]

There are obvious theoretical dangers involved in quickly lowering the blood pressure in severe hypertensives. In cases in which arteriolar sclerosis has prevented the usual dilatation of the vessels accompanying the fall in pressure, these dangers have proved real, both from ischemia and arteriolar thromboses due to slowing of the circulation.[11] Inadvertent lowering of the pressure to shock levels has been disastrous in a significant number of cases. Transient symptoms of cerebral ischemia have been observed, and in some cases permanent damage from cerebral thromboses. Anginal attacks have

[11] Grimson, K. S., et al.: Caution with regard to the use of hexamethonium and "Apresoline," J. A. M. A. **149**: 215–219, 1952.

[12] Page, I. H.: Treatment of essential and malignant hypertension, J. A. M. A. **147**: 1311–1318, 1951.

occurred and in several cases, coronary thromboses. In one case Schroeder [4] observed multiple disseminated coronary thromboses and extensive infarctions. Anuria occurs in the hypotensive crises, and the precipitation of fatal uremia in cases with severe renal involvement has been relatively frequent. The hypotension can usually be combated by suitable stimulants such as Neosynephrine, but these have not always been effective. Epinephrine is not suitable.

Fries et al.[3] have emphasized that such reactions have usually occurred after the initial dose in hypersensitive subjects. This indicates the need for extreme caution in beginning treatment. Such crises, however, have occurred after several weeks of treatment. Patients on a low sodium diet and those who have had an unsuccessful sympathectomy are unusually susceptible. Both drugs should never be administered at the same moment, and they should never be started simultaneously. The dosage of hexamethonium should be established before 1-hydrazinophthalazine is begun.

No evidence of late toxic injury from either drug has been observed after periods of treatment up to 11 months.[9]

Treatment with these drugs is still in the experimental stage, particularly in combination. They are powerful agents, dangerous if clumsily used. They should not be given merely because the blood pressure is elevated, but they should be reserved for cases with significant symptoms or with evidences of advancing arteriolar sclerosis or for cases already in the malignant phase. With rare exceptions the treatment should be started in a hospital and continued there until a reasonably stable dosage is established. Close observation is imperative for an indefinite period after discharge. Expertly handled, these drugs have yielded excellent immediate results, but with less meticulous care they are likely to do more harm than good. The technic of administering them safely is now too cumbersome for extensive use. Although it is improbable that any effective drug of this type will ever be "fool proof," we may hope that drugs will be found which are more uniform in their activity and freer from side effects. Until this has been accomplished and the technic of administration simplified, these drugs are not suitable for promiscuous use.

P. W. C.

# REVIEWS

*Textbook of Orthopaedics.* By M. Beckett Howorth, M.D., Clinical Professor of Orthopedic Surgery, New York University Post-Graduate Medical School; in association with Fritz J. Cramer, M.D., A. Wilbur Duryee, M.D., Donovan J. McCune, M.D., J. William Littler, M.D., and Walter A. Thompson, M.D. 1110 pages; 16.5 × 25.5 cm. W. C. Saunders Company, Philadelphia, Pennsylvania. 1952. Price, $16.00.

Rather than read this book didactically, your reviewer has been using it as a frequent reference book during the past few months and has been pleased to find it very useful and complete in its information. To some it will seem to be unnecessarily long in its text of description and discussion, but I believe this will make it more useful for students and young trainees. The information is accurate and up-to-date and is well arranged in sections written by a group of capable specialists who evidently spent much time collecting the data, as the bibliography is extensive and frequently referred to throughout the book.

Dr. Howorth is to be commended for his courage in attempting so momentous a work and I believe it should be on the shelf of all libraries, practicing orthopedic surgeons and students of orthopedic surgery in school and in training; in fact, it will be useful to anyone practicing medicine, especially surgery, as it is full of basic and fundamental facts for differential purposes.

A. F. V.

*Methods in Medical Research.* Volume 5. A. C. Corcoran, Editor-in-Chief. 394 pages; 14.5 × 22.5 cm. The Year Book Publishers, Inc., Chicago, Illinois. 1952. $7.50.

The volume is divided into three sections. Section I, edited by Lyman C. Craig, consists of physico-chemical methods of separation of biological compounds. These methods are counter-current distribution, paper chromatography, electrophoresis and ultracentrifugation. These methods have stimulated progress in medical research in recent years and promise much for the future.

Section III, edited by Melvin Cohn, also involves separations. These are of immunological substances. The separations are by ethanol fractionation and by precipitin reactions in liquid media and in gels.

Section II, edited by A. C. Corcoran, concerns methods of study of renal function. These include plasma disappearance rates, renal blood flow, body water compartments, bioassay of antidiuretic and diuretic substances and induction of the nephrotic syndrome by anti-kidney serum. Technics for renal studies including indirect blood pressures in rats are presented. Such a discussion of the recent methods of renal study fills a distinct need. The endogenous creatinine clearance study particularly seems to deserve attention of clinicians. While it has certain limitations, it appears to be "superior to either the inulin or urea clearance—as a clinical measure of glomerular filtration rate."

G. E. G.

*The Physiology and Pathology of Hemostasis.* By Armand J. Quick, Ph.D., M.D., Professor of Biochemistry, Marquette University School of Medicine. 188 pages; 15.5 × 24 cm. Lea & Febiger, Philadelphia. 1951. Price, $4.00.

This monograph provides clinicians, physiologists and laboratory workers with a highly readable account of Dr. Quick's contributions and current concepts regarding

blood coagulation, the hemorrhagic diseases, venous thrombosis and the laboratory methods on which the concepts are based. Although less complete than the author's more general monograph of 1942, this book remains a valuable reference. The numerous figures and tables included enhance the understanding of the rather complex subject of hemostasis and the bibliography relevant to the specific content of the book is of value.

The book is divided into two general divisions. The initial section is devoted to the clinical approach to coagulation and its disorders including the hemorrhagic diseases and a new section concerned with venous thrombosis. It is unfortunate that the discussion of venous thrombosis is restricted by the size of the monograph since, in the author's words "(It) presents a major problem in both Medicine and Surgery." The latter portion of the book is composed of brief but concise descriptions of many of the laboratory methods utilized in the study of hemorrhagic disorders, as performed in Dr. Quick's laboratory. This section is particularly valuable as a reference source to those interested in the field.

Dr. Quick, a pioneer in the field of blood coagulation as well as a prolific writer on the subject, maintains a terminology and several concepts of his own which are virtually distinct from those of other authors in this field. The value of much of the present day coagulation literature is diminished for the average reader due to the tendency of many authors to cling to their own terminology thus producing confusing synonyms. The need for a uniform terminology in this field is great. The book is recommended to those interested in the detailed study of blood coagulation.

J. B. W.

*Progress in Fundamental Medicine*. Edited by J. F. A. McManus. 316 pages; 18 × 26 cm. Lea and Febiger, Philadelphia. 1952. Price, $9.00.

This attractive volume contains a series of reviews on subjects of clinical and pathological importance to which new knowledge is currently being added. All of the authors have made original contributions to the subjects they discuss and there is a distinctly personal flavor in many of the discussions.

In his well written chapter on coronary artery disease, Patterson emphasizes his opinion and quotes his evidence that the great majority of coronary occlusions are initiated by intimal hemorrhage. This controversial subject is one that may well repay further extensive scrutiny by other observers. The Mallorys, after a wordy beginning, settle down to good reviews of many hepatic subjects including function tests, biopsy, viral hepatitis, fatty infiltration, ceroid, necroses, the various cirrhoses and primary carcinoma. Klemperer gives a lively account of the history and present concepts of disseminated lupus erythematosus with full discussion of the "hematoxylin bodies," which he has described as diagnostic, and their contained depolymerized desoxyribose nucleic acid (DNA). He discusses the relationship of these to the L.E. cells of Hargraves and to nucleoprotein metabolism. Klemperer does not subscribe to the popular belief that hypersensitivity is the pathogenetic mechanism of disseminated lupus.

Kligman gives a clear and well illustrated account of staining methods in the diagnosis of fungus infections, both superficial and systemic. Special consideration is given the periodic acid-Schiff staining method devised by Hotchkiss and McManus, and Arzac's and the author's modifications of this technic designed to facilitate the demonstration of fungi in tissues. Other topics and their authors are: recent advances in parenteral nutrition with particular reference to protein hydrolysates by Cannon; melanotic tumors of the skin by Cunningham; a survey of technics for the histochemical approach to pathology by McManus; the problem of carcinoma in situ with reference to the human cervix uteri by Stoddard; the recognition of carcinoma in situ of the cervix uteri by Papanicolaou's method by Cuyler; and the non-silica pneumoconioses by Wyatt.

It should be emphasized that these are predominantly pathological treatises; but they all deal with pathology of lively interest to the practicing physician and offer practical as well as stimulating information.

H. J. L. M.

## BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Advances in Internal Medicine.* Volume V. Editors: WILLIAM DOCK, M.D., Long Island College of Medicine, Brooklyn, and I. SNAPPER, M.D., The Mount Sinai Hospital, New York. 464 pages; 23.5 × 15 cm. 1952. The Year Book Publishers, Chicago. Price, $10.50.

*Bacterial and Mycotic Infections of Man.* 2nd Ed. Edited by RENÉ J. DUBOS, Ph.D., The Rockefeller Institute for Medical Research. 886 pages; 26 × 18 cm. 1952. J. B. Lippincott Company, Philadelphia. Price, $7.50.

*Congenital Anomalies of the Heart and Great Vessels.* By MAURICE A. SCHNITKER, B.S., M.D., F.A.C.P., Lt. Col., A.U.S., Medical Consultant, Pacific Theater, World War II, Director of Medicine, St. Vincent's Hospital, etc. 306 pages; 24.5 × 15.5 cm. 1952. Oxford University Press, New York. Price, $8.00.

*Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment.* 3d Ed. Edited by GARFIELD G. DUNCAN, M.D.; with contributions by WALTER BAUER, HUGH R. BUTT, ABRAHAM CANTAROW, GARFIELD G. DUNCAN, FRANK ALEXANDER EVANS, FERDINAND FETTER, JOSEPH M. HAYMAN, JR., ANCEL KEYS, FRIEDRICH KLEMPERER, RACHMIEL LEVINE, EDWARD H. MASON, MAX MILLER, JOHN P. PETERS, J. E. RALL, RULON W. RAWSON, SAMUEL SOSKIN, TOM D. SPIES, CECIL WATSON, ABRAHAM WHITE and PRISCILLA WHITE. 1179 pages; 25 × 17 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $15.00.

*Disorders of the Circulatory System: A Symposium Presented at the Twenty-fourth Graduate Fortnight of The New York Academy of Medicine, October Eighth to Nineteenth, 1951.* Edited by ROBERT L. CRAIG, M.D. 305 pages; 21.5 × 14.5 cm. 1952. The Macmillan Company, New York. Price, $5.50.

*Electrocardiography in Practice.* 3rd Ed. By ASHTON GRAYBIEL, M.D., Captain, Medical Corps, United States Navy, etc.; PAUL D. WHITE, M.D., Executive Director, National Advisory Heart Council, etc.; LOUISE WHEELER, A.M., Executive Secretary, the Cardiac Laboratory, Massachusetts General Hospital; and CONGER WILLIAMS, M.D., Instructor in Medicine, Harvard Medical School, etc. 378 pages; 28 × 20.5 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $10.00.

*Expert Committee on Trachoma: First Report. World Health Organization Technical Report Series No. 59.* 22 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; Agents for U. S. A.: Columbia University Press, International Documents Service, New York. Price, 15 cents.

*Health Programs Digest: An Outline of Selected Plans, Programs and Proposals in the United States, Based on Information Published Prior to December 31, 1951. Public Health Service Publication No. 191.* 146 pages; 26 × 20 cm. (paper-bound). 1952. Federal Security Agency: Public Health Service, Bureau of Medical Services, Division of Medical and Hospital Resources, Washington, D. C. Limited edition, available without charge to those professionally interested.

*Monographs in Medicine, Series I.* Editor: WILLIAM B. BEAN, M.D., Professor and Head of the Department of Medicine, State University of Iowa; Associate Editors: MORTON HAMBURGER, M.D., Associate Professor of Medicine, University of Cincinnati School of Medicine; JOHN A. LEUTSCHER, JR., M.D., Associate Professor of Medicine, Stanford University School of Medicine; and STEWART WOLF, M.D., Professor and Head of the Department of Medicine, University of Oklahoma School of Medicine. 655 pages; 24 × 15.5 cm. 1952. The Williams & Wilkins Company, Baltimore. Price, $12.00.

*Morbus Alzheimer and Morbus Pick: A Genetic, Clinical and Patho-anatomical Study.* By TORSTEN SJÖGREN, HAKON SJÖGREN and ÅKE G. H. LINDGREN. 152 pages; 24.5 × 16.5 cm. (paper-bound). 1952. Ejnar Munksgaard, Copenhagen. Price, 25 Swedish crowns.

*Nutrition and Diet in Health and Disease.* 6th Ed. By JAMES S. MCLESTER, M.D., Professor of Medicine Emeritus, University of Alabama; and WILLIAM J. DARBY, M.D., Ph.D., Professor of Biochemistry and Director of the Division of Nutrition, Vanderbilt University. 710 pages; 24.5 × 16 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $10.00.

*Office Psychiatry: The Management of the Emotionally & Mentally Disturbed Patient.* By LOUIS G. MOENCH, M.D., Assistant Clinical Professor of Medicine and of Psychiatry, University of Utah School of Medicine. 310 pages; 21 × 14.5 cm. 1952. The Year Book Publishers, Inc., Chicago. Price, $6.00.

*Ophthalmic Pathology: An Atlas and Textbook, Published Under the Joint Sponsorship of the American Academy of Ophthalmology and Otolaryngology and the Armed Forces Institute of Pathology.* By JONAS S. FRIEDENWALD, HELENOR CAMPBELL WILDER, A. EDWARD MAUMENEE, T. E. SANDERS, JOHN E. L. KEYES, MICHAEL J. HOGAN and W. C. and ELLA U. OWENS; with the editorial assistance of HELEN KNIGHT STEWARD. 489 pages; 29.5 × 20 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $18.00.

*Practical Dermatology for Medical Students and General Practitioners.* By GEORGE M. LEWIS, M.D., F.A.C.P., Professor of Clinical Medicine (Dermatology), Cornell University Medical College, etc. 328 pages; 25.5 × 16.5 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $7.50.

*Rheumatismus, Klinik und Therapie.* By DR. ERWIN SCHLIEPHAKE. 144 pages; 23 × 15.5 cm. (paper-bound). 1952. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, Brosch. DM 14,– geb. DM 16,–.

*Standard Values in Blood, Being the First Fascicle of a Handbook of Biological Data, Prepared Under the Direction of the Committee on the Handbook of Biological Data, American Institute of Biological Sciences, the National Research Council.* Edited by ERRETT C. ALBRITTON, A.B., M.D., Fry Professor of Physiology, The George Washington University. 199 pages; 28 × 21.5 cm. (paper-bound). 1952. W. B. Saunders Company, Philadelphia. Price, $4.50.

*Vultures Around My Bed.* By IVERS MCCRARY. 54 pages; 19.5 × 14 cm. (paper-bound). 1952. The Trinity House, Mesquite, Texas. Price, $1.00.

*X-Ray Diagnosis of Chest Diseases.* By COLEMAN B. RABIN, M.D., Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, etc. 208 pages; 26 × 17.5 cm. 1952. The Williams & Wilkins Company, Baltimore. Price, $12.00.

# COLLEGE NEWS NOTES

## Elections to Membership in the American College of Physicians

At a meeting of the Board of Regents, held in Philadelphia, November 16, 1952, the following candidates were elected to membership in the College (Fellows indicated in FULL CAPITALS; Associates, Lower Case):

ARTHUR FREDERICK ABT.....Chicago, Ill.
Joseph Edington Acker, Jr.....Knoxville, Tenn.
Milton Ackerman.....Atlantic City, N. J.
Henry Franz Albrecht, Jr.....Troy, N. Y.
Henry Harr Alderfer.....Marion, Ind.
David Hillard Appelman.....Brooklyn, N. Y.
Albert Aranson.....Portland, Maine
Hyman Arenberg.....New York, N. Y.
Charles Andrew Armbrust, Jr.....Houston, Tex.
Clyde Ellis Asbury, Jr.....Wilkes-Barre, Pa. (V.A.)
John Dewitt Ashley, Jr.....Newport, Ark.

Merle Stoner Bacastow.....Worcester, Mass.
Ben Cooke Barnes.....Allentown, Pa.
George Richard Barry.....Monroe, Wis.
BIAGIO BATTAGLIA.....Brooklyn, N. Y.
Frederick Charles Bauer, Jr.....Chicago, Ill.
David Paul Baumann.....Little Rock, Ark.
D. R. BEDFORD.....Topeka, Kans.
PAUL LINCOLN BEDINGER.....Evanston, Ill.
WILLIAM HENRY BEIERWALTES.....Ann Arbor, Mich.
Joseph George Benton.....Forest Hills, N. Y.
Alfred Jacob Berger.....New Britain, Conn.
Norman Sidney Blackman.....Brooklyn, N. Y.
Harry Amerman Bliss.....Portland, Maine
Douglas Booking.....London, Ont., Can.
HENRY DEAN BRAINERD, SR.....San Francisco, Calif.
Otto Brandman.....Newark, N. J.
C(HARLES) RICHARD BRANDT.....Harrisburg, Pa.
Earl Phillip Brannon.....Perry Point, Md. (V.A.)
HENRY JEROME BROCK.....Buffalo, N. Y.
Robert Alexander Broome, Jr.....Orlando, Fla.
Bruce Row Brown.....Framingham, Mass.
Ernest Mack Brown, Jr.....Havertown, Pa.
Edward Gray Brownell.....Winnipeg, Man., Can.
Herschel Louis Browns.....Lakewood, Ohio
Michael Salvatore Bruno.....New York, N. Y.
Morton Samuel Bryer.....New York, N. Y.
EDWARD BUDNITZ.....Worcester, Mass.
CHARLES HOYT BURNETT.....Chapel Hill, N. C.
John Byron Burrows.....Houston, Tex.
Otto Whitmore Burtner.....Miami, Fla.

James Clarence Cain.....Rochester, Minn.
CARLOS CALERO MOLINA.....Panama City, R. P.
MAX CAPLAN.....Meriden, Conn.

PAUL SIMON CAPLAN.....Pittsburgh, Pa.
A. Joseph Cappelletti.....Waterbury, Conn.
HENRY ASHLEY CARR.....New York, N. Y.
THOMAS LYLE CARR.....Iowa City, Iowa
John Randolph Chambliss.....Rocky Mount, N. C.
Raymond Mervin Charnas.....St. Louis, Mo.
Robert Bruno Chodos.....Brookline, Mass. (V.A.)
Norman Anton Christensen.....Rochester, Minn.
THOMAS WILLIAMS CLARK.....Philadelphia, Pa.
Oscar Withers Clarke, Jr.....Gallipolis, Ohio
Edward Osborne Coates, Jr.....Trudeau, N. Y.
Jess Victor Cohn.....Embreeville, Pa.
James Joseph Coll.....Duluth, Minn.
William S. Collens.....Brooklyn, N. Y.
Frank Concilus.....Pittsburgh, Pa.
Francis Place Coombs.....Brooklyn, N. Y.
Morris Coshak.....Waterbury, Conn.
NORMAN LEO CRESSY.....Northampton, Mass.
William Holmes Crosby, Jr.....M.C., U. S. Army

George William Dana.....Baltimore, Md.
Merrill Clark Davenport.....M.C., U. S. Army
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ETHEL FANSON.....Pasadena, Calif.
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Joseph Thomas Schein.....New York, N. Y.
Peritz Scheinberg.....Miami, Fla.
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Christian Elmer Schrock.....Waverly, Iowa
Benjamin Schwartz.....Brooklyn, N. Y. (V.A.)
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Michael Scimeca.....Brooklyn, N. Y.
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Destiny Edmund Storey.....Indianapolis, Ind.
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William Marcellus Straight.....Miami, Fla.

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LUTHER LEONIDAS TERRY.....U. S. Public Health Service
Acors William Thompson.....M.C., U. S. Army
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Walter Thornton Zimdahl.....Buffalo, N. Y.
HYMAN JOSEPH ZIMMERMAN.....Omaha, Nebr. (V.A.)
Nelson Zivitz.....Miami Beach, Fla.
Sidney Nathaniel Zubrow.....Philadelphia, Pa.
Reuben Zucker.....Waterbury, Conn.
Sidney Zuckerman.....Flushing, N. Y.

## A.C.P. Postgraduate Courses, Spring 1953

The Committee on Postgraduate Courses and the Board of Regents on November 16, 1952, adopted the following schedule of courses for the winter and spring of 1953:

No. 1. PATHOLOGY AND PATHOLOGIC PHYSIOLOGY IN INTERNAL MEDICINE: Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation, Euclid Avenue at East 93rd St., Cleveland, Ohio; A. Carlton Ernstene, M.D., F.A.C.P., Director; February 16–21, 1953.

(Minimal Registration, 50;
Maximal Registration, 100)

Fees: A.C.P. Members, $30.00
Non-members, $60.00

*Consulting Committee*

Donald B. Effler, M.D.
John R. Haserick, M.D. (Associate)
John B. Hazard, M.D.
Stanley O. Hoerr, M.D., F.A.C.S.
Fay A. LeFevre, M.D., F.A.C.P.
A. H. Robnett, M.D.
Robert W. Schneider, M.D., F.A.C.P.
Robert D. Taylor, M.D., F.A.C.P.
Walter J. Zeiter, M.D., F.A.C.P.

### Officers of Instruction

John D. Battle, M.D., F.A.C.P., Department of Medicine, Cleveland Clinic.
Charles H. Brown, M.D., F.A.C.P., Department of Gastro-enterology, Cleveland Clinic.
E. N. Collins, M.D., F.A.C.P., Head, Department of Gastro-enterology, Cleveland Clinic.
J. R. Cook, M.D., Department of Endocrinology and Metabolism, Cleveland Clinic.
Arthur C. Corcoran, M.D., Assistant Director, Research Division, Cleveland Clinic.
George Crile, Jr., M.D., F.A.C.S., Department of Surgery, Cleveland Clinic.
Victor G. deWolfe, M.D. (Associate), Department of Cardiovascular Disease, Cleveland Clinic.
Robert S. Dinsmore, M.D., F.A.C.S., Chief of Staff, Division of Surgery, Cleveland Clinic.
William J. Engel, M.D., F.A.C.S., Department of Urology, Cleveland Clinic.
A. Carlton Ernstene, M.D., F.A.C.P., Chief of Staff, Division of Medicine, Cleveland Clinic.
Willis M. Fowler, M.D., F.A.C.P., Professor of Medicine, State University of Iowa College of Medicine, Iowa City, Iowa.
Stanley M. Goldhamer, M.D., F.A.C.P., Clinical Instructor in Medicine, Western Reserve University School of Medicine.
T. Hale Ham, M.D., F.A.C.P., Professor of Medicine, Western Reserve University School of Medicine.
John R. Haserick, M.D. (Associate), Department of Dermatology and Syphilology, Cleveland Clinic.
John B. Hazard, M.D., Head, Department of Pathology, Cleveland Clinic.
Stanley O. Hoerr, M.D., F.A.C.S., Department of Surgery, Cleveland Clinic.

David O. Humphrey, M.D. (Associate), Department of Cardiovascular Disease, Cleveland Clinic.

John W. King, M.D. (Associate), Head, Department of Clinical Pathology, Cleveland Clinic.

Wilhelm J. Kolff, M.D., Research Division, Cleveland Clinic.

Fay A. LeFevre, M.D., F.A.C.P., Department of Cardiovascular Disease, Cleveland Clinic.

Leonard L. Lovshin, M.D. (Associate), Department of Medicine, Cleveland Clinic.

Lawrence J. McCormack, M.D., Department of Pathology, Cleveland Clinic.

E. Perry McCullagh, M.D., F.A.C.P., Head, Department of Endocrinology and Metabolism, Cleveland Clinic.

Robert D. Mercer, M.D., Head, Department of Pediatrics, Cleveland Clinic.

Max Miller, M.D., Assistant Professor of Medicine, Western Reserve University School of Medicine.

Irvine H. Page, M.D., F.A.C.P., Director, Research Division, Cleveland Clinic.

William L. Proudfit, M.D., F.A.C.P., Department of Cardiovascular Disease, Cleveland Clinic.

H. R. Rossmiller, M.D., F.A.C.P., Department of Gastroenterology, Cleveland Clinic.

Arthur L. Scherbel, M.D., Department of Medicine, Cleveland Clinic.

Robert W. Schneider, M.D., F.A.C.P., Department of Endocrinology and Metabolism, Cleveland Clinic.

Penn G. Skillern, M.D., Department of Endocrinology and Metabolism, Cleveland Clinic.

F. Mason Sones, M.D., Department of Cardiovascular Disease, Cleveland Clinic.

Viola Startzman, M.D., Department of Pediatrics, Cleveland Clinic.

Robert D. Taylor, M.D., F.A.C.P., Research Division, Cleveland Clinic.

Ray A. VanOmmen, M.D., Department of Cardiovascular Disease, Cleveland Clinic.

H. Scott VanOrdstrand, M.D., F.A.C.P., Head, Department of Pulmonary Disease, Cleveland Clinic.

Richard N. Westcott, M.D., Department of Cardiovascular Disease, Cleveland Clinic.

John F. Whitman, M.D., Department of Cardiovascular Disease, Cleveland Clinic.

Carl J. Wiggers, M.D., F.A.C.P., Professor of Physiology, Western Reserve University School of Medicine.

Guy Williams, Jr., M.D., Department of Neurology and Psychiatry, Cleveland Clinic

This course will place emphasis on pathologic anatomy and current concepts of pathologic physiology in systemic disease. The principal objective will be to stress the relationship between pathology, pathologic physiology, and clinical diagnosis and treatment. The major subjects to be presented will be in the fields of cardiovascular and renal disease, pulmonary disease, gastro-enterology, hematology, endocrinology, and metabolic diseases. The course will include lectures, clinical demonstrations, pathology conferences, and question and answer panels.

The lectures will be given in the Founders' and Staff Room of the Cleveland Clinic.

*Hotel Accommodations:* Accommodations may be obtained at the Wade Park Manor, East 107th Street and Park Lane, Cleveland 6. Mr. Owen C. Obetz, General Manager. Single rooms, $5.50 to $7.00 per day; twin-bedded rooms, $9.00 to $11.00 per day; suites, $15.00 per day and up.

A complimentary reception and dinner for members of the course and their wives will be given at the Wade Park Manor on the first evening, February 16.

OUTLINE OF COURSE

*Monday, February 16*

A.M. Session

8:00– 8:50 Registration.
8:50– 9:00 Orientation.
Dr. Ernstene.

CARDIOVASCULAR DISEASE

9:00– 9:30 Pathogenesis of Congestive Heart Failure.
Dr. Westcott.
9:30–10:15 The Mechanism of Edema.
Dr. Wiggers.
10:15–10:45 Cardiac Arrhythmias and Their Treatment.
Dr. Humphrey.
10:45–11:00 Intermission.
11:00–11:30 Coronary Artery Disease.
Dr. Ernstene.
11:30–12:00 Treatment of Congestive Heart Failure.
Dr. Proudfit.
12:00–12:30 Question and Answer Panel.
12:30– 1:30 Luncheon—Courtesy of the Cleveland Clinic.

P.M. Session

HYPERTENSION AND RENAL DISEASE

1:30–2:00 Pathogenesis of Essential Hypertension.
Dr. Page.
2:00– 2:30 Renal Function Tests.
Dr. Taylor.
2:30– 3:15 Fluid and Electrolyte Balance.
Dr. Corcoran.
3:15– 3:30 Intermission.
3:30– 4:00 Anuria and Uremia.
Dr. Kolff.
4:00– 5:00 Pathology Conference: Renal Disease.
Drs. Hazard, McCormack, Corcoran and Taylor.
5:00– 5:30 Question and Answer Panel.
6:30 Reception and dinner for members of the course and their wives at the Wade Park Manor.

*Tuesday, February 17*

A.M. Session

ARTERIOSCLEROSIS, CARDIAC CATHETERIZATION AND PULMONARY DISEASE

8:00– 9:00 Clinical Conference—Pathology and Pathologic Physiology of Peripheral Arterial Disease.
Drs. LeFevre, deWolfe and Hazard.
9:00– 9:30 Pathogenesis of Arteriosclerosis.
Dr. Page.
9:30–10:15 Differential Diagnosis in Congenital Heart Disease.
Dr. Sones.
10:15–10:30 Intermission.
10:30–10:50 Mitral Commissurotomy: Pre- and Post-operative Studies.
Dr. Sones.

10:50–11:30 Pulmonary Function Tests and Pulmonary Emphysema.
Dr. Westcott.
11:30–12:00 The Pneumoconioses.
Dr. VanOrdstrand.
12:00–12:30 Question and Answer Panel.
12:30– 1:30 Luncheon—Courtesy of the Cleveland Clinic.

P.M. Session

GASTRO-INTESTINAL DISEASE

1:30– 2:15 Peptic Ulcer and Its Complications.
Dr. Collins.
2:15– 2:45 Disorders of External Secretory Function of the Pancreas.
Dr. Rossmiller.
2:45– 3:15 Differential Diagnosis of Jaundice.
Dr. Brown.
3:15– 3:30 Intermission.
3:30– 4:00 Cirrhoses of the Liver and Their Complications.
Dr. Rossmiller.
4:00– 4:30 Disturbances of Intestinal Absorption.
Dr. Brown.
4:30– 5:00 Question and Answer Panel.

*Wednesday, February 18*

A.M. Session

GASTRO-INTESTINAL DISEASE

8:00– 9:00 Pathology Conference—Diseases of the Liver.
Drs. Hazard, McCormack and Rossmiller.
9:00– 9:30 Acute Intestinal Obstruction.
Dr. Hoerr.
9:30–10:00 Problems of Biliary Tract Surgery.
Dr. Dinsmore.
10:00–10:20 Urologic Disease as a Cause of Gastro-intestinal Symptoms.
Dr. Engel.
10:20–10:45 The Irritable Colon.
Dr. Collins.
10:45–11:00 Intermission.
11:00–11:30 Primary Amyloidosis.
Dr. VanOmmen.
11:30–12:00 Systemic Lupus Erythematosus.
Dr. Haserick.
12:00–12:30 Question and Answer Panel.
12:30– 1:30 Luncheon—Courtesy of the Cleveland Clinic.

P.M. Session

1:30– 2:15 Headache.
Dr. Lovshin.
2:15– 2:45 Convulsive Disorders in Infancy and Childhood.
Dr. Mercer.
2:45– 3:15 The Muscular Dystrophies and Muscular Atrophies.
Dr. Williams.
3:15– 3:30 Intermission.
3:30– 4:00 Reticulo-Endothelial Syndromes.
Dr. Mercer.

4:00– 4:30 The Lipomatoses and Lipodystrophies.
Dr. Whitman.
4:30– 5:00 Question and Answer Panel.

*Thursday, February 19*

A.M. Session

HEMATOLOGY

8:00– 9:00 Pathology Conference—The Leukemias and Malignant Lymphomas.
Drs. Hazard, McCormack and Battle.
9:00– 9:30 Diagnostic Methods in the Classification of Anemias.
Dr. Ham.
9:30–10:00 The Physiologic Mechanisms of the Hemolytic Anemias.
Dr. Ham.
10:00–10:45 Sickle Cell Anemia and Mediterranian Anemia.
Dr. Fowler.
10:45–11:00 Intermission.
11:00–11:30 Polycythemia.
Dr. Fowler.
11:30–12:00 Myeloid Metaplasia.
Dr. Battle.
12:00–12:30 Question and Answer Panel.
12:30– 1:30 Luncheon—Courtesy of the Cleveland Clinic.

P.M. Session

1:30– 2:00 The Macrocytic Anemias.
Dr. Fowler.
2:00– 2:30 Hypochromic Anemia.
Dr. Goldhamer.
2:30– 3:00 Purpura and Hemophilia.
Dr. Battle.
3:00– 3:30 Erythroblastosis.
Dr. Startzman.
3:30– 3:45 Intermission.
3:45– 4:05 Multiple Myeloma.
Dr. Battle.
4:05– 4:30 Transfusion Reactions.
Dr. King.
4:30– 5:00 Question and Answer Panel.

*Friday, February 20*

A.M. Session

ENDOCRINOLOGY AND METABOLIC DISEASES

8:00– 9:00 Pathology Conference: Diseases of the Pancreas.
Drs. Hazard, McCormack and Skillern.
9:00– 9:30 Principal Pathways of Intermediary Metabolism.
Dr. Corcoran.
9:30–10:00 Hypoglycemia.
Dr. Skillern.
10:00–10:30 The Role of Phosphatase.
Dr. Cook.
10:30–10:45 Intermission.
10:45–11:30 Diabetic Acidosis and Coma, with Comments on the Use of Fructose in Therapy.
Dr. Miller.

11:30–12:00 Hyperparathyroidism.
Dr. Schneider.
12:00–12:30 Question and Answer Panel.
12:30– 1:30 Luncheon—Courtesy of the Cleveland Clinic.

P.M. Session
1:30– 2:00 Pathology of Diseases of the Thyroid Gland.
Dr. Crile.
2:00– 2:45 Iodine Metabolism and the Action of Antithyroid Drugs.
Dr. Cook.
2:45– 3:15 Hypothyroidism and Myxedema.
Dr. Skillern.
3:15– 3:30 Intermission.
3:30– 4:00 Obesity and the General Principles of Fat Metabolism.
Dr. Schneider.
4:00– 4:30 Clinical Aspects of Disturbed Pituitary Function.
Dr. McCullagh.
4:30– 5:00 Question and Answer Panel.

*Saturday, February 21*

A.M. Session

ENDOCRINOLOGY AND METABOLIC DISEASES

8:00– 9:00 Pathology Conference: The Adrenals, Ovaries and Testes.
Drs. Hazard, McCormack and McCullagh.
9:00– 9:30 Diagnosis and Treatment of Pheochromocytoma.
Dr. Scherbel.
9:30–10:00 Addison's Disease.
Dr. McCullagh.
10:00–10:45 Adrenal Cortical Hyperfunction.
Dr. Schneider.
10:45–11:00 Intermission.
11:00–11:30 Therapeutic Effects of Estrogens and Androgens.
Dr. McCullagh.
11:30–12:30 Question and Answer Panel. (A Review of the Course.)

No. 2. CARDIOVASCULAR DISEASE: University of Southern California School of Medicine, Los Angeles, Calif.; George C. Griffith, M.D., F.A.C.P., Director; March 2–7, 1953.

No. 3. INTERNAL MEDICINE: Cornell University Medical College and The New York Hospital, New York, N. Y.; David P. Barr, M.D., F.A.C.P., Director; March 9–13, 1953.

No. 4. INTERNAL MEDICINE: Mayo Clinic and Foundation, Rochester, Minn.; Arlie R. Barnes, M.D., F.A.C.P., Hugh R. Butt, M.D., F.A.C.P., Edgar V. Allen, M.D., F.A.C.P., and William H. Dearing, M.D., F.A.C.P., Co-directors; March 23–28, 1953.

No. 5. CARDIOVASCULAR DISEASE: Philadelphia Institutions, Philadelphia, Pa.; William G. Leaman, M.D., F.A.C.P., Director; April 27-May 2, 1953.

No. 6. INTERNAL MEDICINE: The Pennsylvania Hospital, Philadelphia, Pa.; Garfield G. Duncan, M.D., F.A.C.P., Director; May 11–16, 1953.

No. 7. INTERNAL MEDICINE: University of Oregon Medical School, Portland, Ore.; Howard P. Lewis, M.D., F.A.C.P., Director; May 18–22, 1953.

No. 8. ELECTROCARDIOGRAPHY; BASIC PRINCIPLES AND INTERPRETATION: Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D. (Associate), Director; Date to be announced.

A course in ALLERGY at the University of Pittsburgh School of Medicine under the directorship of Leo H. Criep, M.D., F.A.C.P., is held in reserve as an alternate provided any unforeseen problem arises which may postpone any one of the eight formal courses announced.

The detailed Postgraduate Bulletin will be published and mailed to all members of the College during January. Non-members may have their names placed on the mailing list on request. The matriculation fees for each course will be: $30.00 to A.C.P. Members; $60.00 to Non-members. All inquiries, registrations, etc., should be addressed to The American College of Physicians (not to the institutions or to the directors), 4200 Pine St., Philadelphia 4, Pa.

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### Coming A.C.P. Regional Meetings

EASTERN PENNSYLVANIA, at Philadelphia, January 16, 1953; Dr. Thomas McMillan, Governor.

COLORADO, at Denver, February 17, 1953; Dr. C. F. Kemper, Governor.

VIRGINIA, at Hampton, February 26, 1953; Dr. Charles M. Caravati, Governor.

DELAWARE, at Wilmington, February 27, 1953; Dr. Lemuel C. McGee, Governor.

NEBRASKA, at Omaha, February 28, 1953; Dr. Joseph D. McCarthy, Governor.

KANSAS, at Kansas City, March 20, 1953; Dr. William C. Menninger, Governor.

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### Midwest Regional Meeting

The Midwest Regional Meeting embracing the States of Indiana, Illinois, Iowa, Michigan, Minnesota, Ohio and Wisconsin, was held at the Congress Hotel, Chicago, November 22, 1952, under the General Chairmanship of Dr. Howard Wakefield, Governor for Northern Illinois, and with the able coöperation of the Governors of the participating states. Abstracts of all papers presented on the program and of titles offered, but for which no adequate time was available, were published in booklet form and distributed to all members in attendance and later sent to all members who were absent. The attendance (figures given below) was most gratifying. At the conclusion of the Banquet in the evening, a handsome wrist watch was presented to Mr. E. R. Loveland, Executive Secretary of the College, engraved, "To E. R. Loveland with love and devotion from all the Members of the Midwest Regional States."

Attendance—Midwest Regional Meeting

| *State* | Fellows | Associates | Guests | Total |
|---|---|---|---|---|
| Northern Illinois | 86 | 46 | 128 | 260 |
| Southern Illinois | 13 | 13 | 8 | 34 |
| Indiana | 22 | 13 | 11 | 46 |
| Iowa | 10 | 5 | 7 | 22 |
| Michigan | 33 | 7 | 11 | 51 |
| Minnesota | 7 | 5 | 3 | 15 |
| Ohio | 18 | 8 | 7 | 33 |
| Wisconsin | 25 | 13 | 20 | 58 |
| Other States | 5 | 4 | 9 | 18 |
| Grand Total | 219 | 114 | 204 | 537 |

### Southeastern Regional Meeting, Havana, November 7–8, 1952

For the first time in the history of the College the Southeastern Regional Meeting, comprising the States of Florida, Georgia, Alabama and South Carolina, and the Commonwealth of Cuba, held the annual Regional Meeting in Havana, Cuba, November 7–8, with an added day of entertainment on November 9. Dr. José J. Centurión, F.A.C.P., Governor for Cuba, was in charge of the program, ably helped by the Governors of the participating states, Dr. Carter Smith, F.A.C.P., Governor for Georgia, Dr. E. Dice Lineberry, F.A.C.P., Governor for Alabama, and his alternate, Dr. D. O. Wright, F.A.C.P., Dr. William C. Blake, F.A.C.P., Governor for Florida, and Dr. Robert Wilson, F.A.C.P., Governor for South Carolina. For the United States, Dr. Carter Smith was Chairman of the Committee on Scientific Program and for Cuba, Dr. Angel Vieta; Dr. J. Manuel Viamonte, F.A.C.P., was Chairman of the Committee on Hotel and Transportation, and Dr. Felix Hurtado, F.A.C.P., was Chairman of the Committee on Banquet and Entertainment.

The meeting was the most largely attended Southeastern Regional Meeting that has been held, there being some 200 physicians and in many instances, their wives, in attendance. The program was an excellent one from the scientific standpoint and the entertainment features were superb.

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### Passes, Railroad Physicians, Southeastern Territory

The Pass Committee of the Southeastern President's Conference has advised that transportation without charge to personal quotas may be issued to railroad physicians attending annual meetings of the American College of Physicians.

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### Future Meetings, American Academy of General Practice

The American Academy of General Practice announces the following dates for future Annual Sessions, hoping thereby to avoid conflict in dates among the Annual Meetings of other organizations:

1953—March 23–26, St. Louis
1954—March 22–25, Cleveland
1955—March 28–31, Los Angeles (tentative)

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### University of California Sponsors Course on Pulmonary Function

A Seminar on Pulmonary Function, sponsored by the University of California School of Medicine in coöperation with the American Trudeau Society and the Medical Faculty of Stanford University, will be held Feb. 6–8 in Toland Hall, University of California Hospital, San Francisco. Dr. Dickinson W. Richards, Jr., F.A.C.P., New York, one of the two guest speakers, will talk on "Cardiac Changes of Pulmonary Origin," "Dyspnea and the Control of Respiration," and "Alveolar Capillary Block: Clinical and Physiological Characteristics." Faculty members include Dr. H. Corwin Hinshaw, Sr., F.A.C.P., and Dr. Harold G. Trimble, F.A.C.P., of Stanford University; Dr. Maurice Eliaser, Jr., F.A.C.P., Dr. Stacy R. Mettier, F.A.C.P., College Governor for Northern California, Dr. John J. Sampson, F.A.C.P., Dr. Sidney J. Shipman, F.A.C.P., and Dr. Maurice Sokolow, F.A.C.P., all of the University of California.

### Endocrine and Metabolic Disease Is Subject of Intensive Course

"The Dynamics of Endocrine and Metabolic Disease," an intensive course designed to emphasize clinical physiology, diagnosis and treatment, will be given Feb. 2–7 in the Administration Building of the Highland-Alameda County Hospital, Oakland, Calif. Presented under the joint auspices of the Committee for Graduate Medical Education of the Alameda-Contra Costa Medical Association and the Institute for Metabolic Research of the Highland-Alameda County Hospital, the course will include such subjects as: carbohydrate, protein, lipid, acid-base, fluid, and electrolyte metabolism; the pituitary, thyroid, adrenal, and parathyroid glands; the gonads, and clinical physiology of the liver. Included on the faculty are: Dr. Leela S. Craig, F.A.C.P., and Dr. Gordon E. Hein, F.A.C.P., Professor Emeritus, University of California School of Medicine; Dr. Laurance W. Kinsell, F.A.C.P., Institute for Metabolic Research; Dr. Eaton M. MacKay, F.A.C.P., Permanente Foundation; Dr. Albert H. Rowe, F.A.C.P., Highland-Alameda County Hospital, and Dr. Dwight L. Wilbur, F.A.C.P., College Regent, Stanford University School of Medicine.

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### "Recent Advances in Diagnosis" to Be Presented by the University of Minnesota

The University of Minnesota will present a continuation course in "Recent Advances in Diagnosis for Internists" at the Center for Continuation Study on February 16–18. Recent developments in the fields of cardiology, respiratory disease, renal disease, hematology, gastro-enterology and endocrinology will be emphasized. Under the direction of Dr. C. J. Watson, F.A.C.P., Professor and Director of the Department of Medicine, a guest faculty that includes the following has been assembled: Dr. Carl V. Moore, F.A.C.P., Professor, Department of Medicine, Washington University School of Medicine, St. Louis; Dr. Thomas E. Machella, F.A.C.P., Assistant Professor, Department of Medicine, and Associate in Physiology, University of Pennsylvania School of Medicine, and Chief of Gastro-Intestinal Clinic, Hospital of the University of Pennsylvania, Philadelphia; and Dr. William W. Engstrom (Associate), Associate Professor, Department of Medicine, Marquette University School of Medicine, and Director, Metabolism Section, Milwaukee County Hospital.

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### University of Pennsylvania Graduate School of Medicine and Pennsylvania Hospital to Create Medical Center

The University of Pennsylvania Graduate School of Medicine and the Pennsylvania Hospital signed an agreement Nov. 1, 1952, proposing a new Medical Center for clinical care, research and graduate medical education. At the completion of the proposed expansion program, the teaching and research activities and the hospital facilities of the Graduate School of Medicine will be transferred to the Pennsylvania Hospital, where an $8,000,000 building program is contemplated. Under this new program, approximately 130,000 square feet of floor space will be provided for the teaching and research purposes of the School, which will then have modern classrooms, teaching laboratories and research facilities. Patient care and clinical services now offered by the University's Graduate Hospital will be transferred to the new facilities at Pennsylvania Hospital, and the money obtained from the sale of the Graduate Hospital will be added to the building fund of the Pennsylvania Hospital, which now totals $2,000,000. Each institution, however, will preserve its own autonomy, and a joint administrative board is to be formed.

### Alpha Omega Alpha Honor Medical Society Installs Chapter at Hahnemann Medical College and Hospital

Alpha Omega Alpha Honor Medical Society installed a Chapter at the Hahnemann Medical College and Hospital of Philadelphia on November 20, 1952. The ceremonies took place at the Philadelphia Country Club. Dr. Charles L. Brown, F.A.C.P., Dean of Hahnemann, was Chairman of the meeting. Dr. Walter L. Bierring, F.A.C.P., National President of Alpha Omega Alpha, conferred the Charter, and Dr. Josiah J. Moore, F.A.C.P., National Secretary-Treasurer of Alpha Omega Alpha, formally installed the Chapter and presented Keys and Certificates, and delivered the Charge to the new Chapter.

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Colonel Ryle A. Radke, Sr., (MC), USA, F.A.C.P., received the annual Sir Henry Wellcome Award at the annual dinner of the Association of Military Surgeons in Washington, D. C., Nov. 19, 1952. Colonel Radke, who won the award for his essay on "The Military Significance of Amebiasis," is Chief of Medical Service at the Tokyo Army Hospital in Japan.

At the same time, Brigadier General James Stevens Simmons, (MC), USA (Retired), F.A.C.P., was awarded the 1952 Gorgas Medal for "distinquished service in preventive medicine for the armed forces." General Simmons is Dean of the Harvard School of Public Health and was formerly wartime Chief of Preventive Medicine in the Army.

Colonel Ralph M. Thompson, (MC), USAF, F.A.C.P., received the Seaman Prize for his essay on the treatment of radiation injury.

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Dr. Willard O. Thompson, F.A.C.P., Chicago, was chosen the Distinguished Service Award Recipient for 1952 by the Mississippi Valley Medical Society at the annual meeting held in St. Louis in October, 1952. Managing Editor of the *Journal of Clinical Endocrinology*, Dr. Thompson received the gold medal and a certificate as one "who has rendered unusual and distinctive service to the medical profession."

Dr. Walter C. Alvarez, F.A.C.P., Chicago, received the honor award of the American Medical Writers' Association at the annual meeting, which was held in conjunction with the M.V.M.S. session. Dr. Alvarez likewise received a gold medal and certificate. Dr. Alvarez also addressed the annual meeting of the American Academy of Dermatology and Syphilology which met in Chicago last month. His topic was "Urticaria—Due to Food or Nerves?"

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Dr. Carroll C. LaFleur Birch, F.A.C.P., Professor of Medicine at the University of Illinois College of Medicine, was honored as the Medical Woman of the Year at the annual joint meeting of the American Medical Women's Association and the Chicago Women's Bar Association. Dr. Birch, speaking on "A Year in India," addressed the banquet of the meeting, which was held in Colorado Springs, Colo., Nov. 29–Dec. 1. Dr. Birch recently returned to Chicago from India, where she spent a year as Dean of the Lady Hardinge Medical College in New Delhi.

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Dr. Arthur H. Sanford, F.A.C.P., Rochester, Minn., has received a scroll of merit from the American Society of Clinical Pathologists. The presentation was made during the 31st annual meeting of the Society in Chicago, Oct. 14–17, 1952.

At the organizational meeting of the Friends of the Armed Forces Medical Library, held in Washington, D. C., Oct. 24, 1952, Dr. Robert M. Stecher, F.A.C.P., Cleveland, was elected to a two-year term as Secretary-Treasurer. Dr. Edward H. Cushing, F.A.C.P., Washington, D. C., and Dr. Edward B. Krumbhaar, F.A.C.P., Philadelphia, were elected to the Executive Committee for similar terms.

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Dr. Charles William Smith, F.A.C.P., Harrisburg, was elected First Vice President of the Medical Society of the State of Pennsylvania at the annual meeting held in Philadelphia Sept. 29–Oct. 3, 1952. Dr. Malcolm W. Miller, F.A.C.P., Philadelphia, was reëlected Assistant Secretary-Treasurer, and Dr. Wilbur E. Flannery (Associate), New Castle, was named Vice Speaker of the House of Delegates.

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Meeting in Savannah, Sept. 12–13, 1952, the Georgia Heart Association elected Dr. Thomas L. Ross, Jr., F.A.C.P., Macon, President, and voted Dr. Joseph C. Massee, F.A.C.P., Atlanta, President-Elect.

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Dr. Eugene H. Drake, F.A.C.P., Portland, was recently elected President of the Maine Medical Association at the annual meeting in Rockland.

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Dr. Ralph Bowen, F.A.C.P., Houston, Tex., was elected President of the Section on Allergy at the Southern Medical Association Meeting, which convened in Miami, Fla., November 10, 1952.

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Dr. William Branch Porter, F.A.C.P., Professor of Medicine at the Medical College of Virginia, Richmond, was honored on October 23 by his former residents, in the founding of the William Branch Porter Society. A scroll presented to Doctor Porter read: "In recognition of his many years of devoted service, unfailing interest, and inspirational teaching as professor of medicine at the Medical College of Virginia, we, his former residents, honor our esteemed teacher . . . by founding the William Branch Porter Society."

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The Association of American Physicians has recently elected the following officers: President, Dr. William S. McCann, F.A.C.P., Rochester, N. Y.; Vice President, Dr. Joseph T. Wearn, F.A.C.P., Cleveland; Secretary, Dr. W. Barry Wood, Jr., F.A.C.P., St. Louis; Treasurer, Dr. Francis C. Wood, F.A.C.P., Philadelphia; Recorder, Dr. Cecil J. Watson, F.A.C.P., Minneapolis.

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Meeting recently in New York, the American Congress of Physical Medicine elected Dr. Walter M. Solomon, F.A.C.P., Cleveland, President; Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., Treasurer, and Dr. Walter J. Zeiter, F.A.C.P., Cleveland, Executive Director.

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Dr. William A. D. Anderson, F.A.C.P., Milwaukee, took office Jan. 1, 1953, as Vice President of the College of American Pathologists.

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Dr. H. Phillip Hampton, F.A.C.P., Tampa, has recently been appointed Chairman of the Committee on Legislation and Public Policy of the Florida Medical Association.

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Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, has recently been elected to the Executive Committee of the newly organized Section on Clinical Cardiology of the American Heart Association.

Dr. John I. Marker, F.A.C.P., Davenport, Iowa, has recently been elected President of the Mississippi Valley Medical Society. At the same time, Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., was reëlected Secretary-Treasurer. The 1953 meeting of this Society will be held in Springfield, Ill., Sept. 23–25; the 1954 meeting at Chicago, Sept. 22–24.

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Dr. Louis Mark, F.A.C.P., Columbus, Ohio, speaking on "Lung Biopsy," was among the out-of-state speakers at a Symposium on Coal Miner's Pneumoconiosis, held in Elkins, W. Va., Nov. 24, 1952. Dr. George R. Maxwell, F.A.C.P., Morgantown, was moderator of the meeting.

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Dr. Oscar A. Sander, F.A.C.P., Milwaukee, served as chairman of the medical conference at the annual meeting of the Industrial Hygiene Foundation of America, Inc., when the society met in Pittsburgh Nov. 19–20, 1952. Dr. R. Emmet Kelly, F.A.C.P., St. Louis, was one of the participants in a panel on "How to Apply Our Present Knowledge."

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Dr. David T. Smith, F.A.C.P., Durham, N. C., delivered the sixth A. Walter Suiter Lecture on "Pulmonary Mycotic Infections: Their Differential Diagnosis and Treatment" on Nov. 6, 1952, in New York City. Sponsored by the Committee on Public Health Relations of the New York Academy of Medicine, the lecture was held in observance of the semicentennial of the New York Tuberculosis and Health Association. As part of the fifty-year celebration itself, held in the Hotel Statler in New York on Nov. 21, 1952, Dr. Carl Muschenheim, F.A.C.P., New York, presented a paper entitled "Place of Antimicrobial Therapy in Tuberculosis."

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Under the presidency of Dr. Joseph J. Combs, F.A.C.P., the Raleigh (North Carolina) Academy of Medicine presented its annual symposium, "The Diagnosis and Treatment of Cancer," Nov. 7, 1952. One of the guest speakers was Dr. Mavis P. Kelsey, F.A.C.P., Houston, Tex., who discussed "Terminal Care of the Cancer Patient."

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Under the auspices of the Chicago Heart Association, an all-day conference, "Heart in Industry," was held at the Palmer House on Nov. 13, 1952. Speakers and their subjects included: Dr. Irvine H. Page, F.A.C.P., Cleveland, "High Blood Pressure in Industry"; Dr. Norman Plummer, F.A.C.P., New York, "Rheumatic Hearts Can Work," and Dr. Edward M. Kline, F.A.C.P., Cleveland, "The Industrial Physician Can Help." Dr. Louis N. Katz, F.A.C.P., Chicago, moderated the afternoon discussions.

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Dr. E. Cowles Andrus, F.A.C.P., Baltimore, addressed the Boston University chapter of Alpha Omega Alpha on Nov. 13, 1952. His topic was "Surgery of Mitral Stenosis and Its Physiological Consequences."

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Dr. Herrman L. Blumgart, F.A.C.P., Boston, speaking on "The Pathologic Physiology of Coronary Heart Disease," delivered the annual William E. Lower Lecture at the Academy of Medicine in Cleveland, Nov. 21, 1952.

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Participating in a symposium on antibiotics, sponsored by the Academy of Medicine of Cincinnati on Nov. 11, 1952, were Dr. Chester S. Keefer, F.A.C.P., Boston, College Governor for Massachusetts, and Dr. Morton Hamburger (Associate), Cincinnati.

Dr. Julius L. Wilson, F.A.C.P., Philadelphia, acted as moderator for the scientific program at the annual meeting of the Connecticut Trudeau Society, which was held in New Haven, Nov. 20, 1952.

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Dr. Paul B. Beeson, F.A.C.P., Atlanta, Ga., Dr. Howard B. Sprague, F.A.C.P., Brookline, Mass., and Dr. Thaddeus S. Danowski, F.A.C.P., Pittsburgh, were among the guest lecturers on cardiovascular disease in a monthly series sponsored by the Stamford (Conn.) Heart Association in Fairfield County.

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Dr. Joseph M. Hayman, Jr., F.A.C.P., Cleveland, spoke on "Medical Diseases of the Kidney" before the Cincinnati Academy of Medicine on Nov. 18, 1952.

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Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, presented a paper on "Geriatrics and the Dentist and Psychosomatic Aspects of Dentistry" at the meeting of the Pennsylvania Association of Dental Surgeons on Nov. 11, 1952.

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Dr. J. Shirley Sweeney, F.A.C.P., Gainesville, Tex., recently lectured in Norman, Okla., on "The Answer to Diabetes in Oklahoma." The address was a feature of the program of the twelfth annual meeting of the Oklahoma Public Health Association.

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Dr. Herman Beerman, F.A.C.P., Philadelphia, was one of the participants in a Conference on Pemphigus and the Bullous Dermatoses, sponsored Nov. 21–22, 1952, by the University of Minnesota, Minneapolis.

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The Surgeon General of the U. S. Public Health Service, Dr. Leonard A. Scheele, F.A.C.P., delivered the first C.-E. A. Winslow Lecture at the Yale University School of Medicine on Nov. 14. "Looking Ahead in World Health" was the topic, and in his talk Dr. Scheele evaluated the special opportunities in the United States with respect to education, training, health and hospital practices.

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Dr. James M. Moss (Associate), Washington, D. C., addressed the Montgomery County (Md.) Medical Society on November 18, 1952. His subject was "The Diagnosis and Management of Diabetes." Dr. Moss has been recently promoted to Assistant Clinical Professor of Medicine at Georgetown University.

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Dr. Charles F. Wilkinson, Jr., F.A.C.P., New York, delivered the 36th Mellon Lecture on "Present Concepts of Atherosclerosis" before the Society for Biological Research of the School of Medicine, University of Pittsburgh, Nov. 5, 1952.

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Dr. George C. Griffith, F.A.C.P., Pasadena, Calif., addressed the yearly meeting of the Washington Academy of General Practice, held in Wenatchee, Oct. 31–Nov. 2. His various subjects were: "What Is New in the Field of Cardiovascular Diseases," "Selection of Patients for Mitral Commissurotomy," "Use of Anticoagulants in Congestive Heart Failure and Coronary Artery Disease," and "Coronary Artery Disease and Its Management."

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Dr. Edward L. Bortz, F.A.C.P., Philadelphia, College Regent, gave the annual Alphonse M. Schwitalla Lecture at the St. Louis University School of Medicine, Oct. 16, 1952. Dr. Bortz's lecture, sponsored by the Beta of Missouri Chapter of Alpha Omega Alpha Honorary Medical Society, was entitled "The Schwitalla Touch in American Medicine."

Dr. Edgar A. Hines, Jr., F.A.C.P., Rochester, Minn., was one of the participants in a Symposium on Peripheral Vascular Diseases that was part of the program of the second annual meeting of the Congress of Neurological Surgeons, held in Chicago, Nov. 6–8, 1952.

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Dr. Wesley W. Spink, F.A.C.P., Minneapolis, College Governor for Minnesota, has recently returned from Spain, where he advised the government on methods of eradicating brucellosis from livestock. Dr. Spink is director of the Brucellosis Research Center of the World Health Organization.

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Dr. Jacques Genest, F.A.C.P., has recently concluded for the Government of the Province of Quebec (Canada) a survey of the Research Institutes and of the main medical centers in the countries of Western Europe. He spent a year traveling in the various countries, but spending most of his time in England and France, meeting the leading physicians and scientists of Europe. His report now will be concluded and presented to the Government of Quebec.

Dr. Genest is now at the Hotel-Dieu Hospital of Montreal, where he has accepted a full-time position as Director of a new Department of Clinical Research.

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Dr. Raymond Wooldridge Swinney, F.A.C.P., Long Beach, Calif., has recently been elected as medical member of the Board of Directors of Long Beach Community Hospital. Dr. Swinney attended the Fourth Inter-American Congress of Cardiology at Buenos Aires in September as a delegate from the California Heart Association, and was the only representative from Southern California at this meeting.

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Dr. Claude-Starr Wright (Associate), Columbus, Ohio, was a member of the guest faculty that presented the second annual regional postgraduate courses sponsored by the Speakers Bureau Committee of the Nebraska State Medical Association. The courses, which were held Nov. 17–22, 1952, were given in Scottsbluff, North Platte, McCook, Grand Island, Norfolk and Beatrice.

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Dr. Durwood J. Smith (Associate) has been appointed Professor of Pharmacology and Chairman of the Department of Pharmacology at the University of Vermont College of Medicine. A medical graduate of Syracuse University, Dr. Smith was previously associated with the University of Rochester since 1946.

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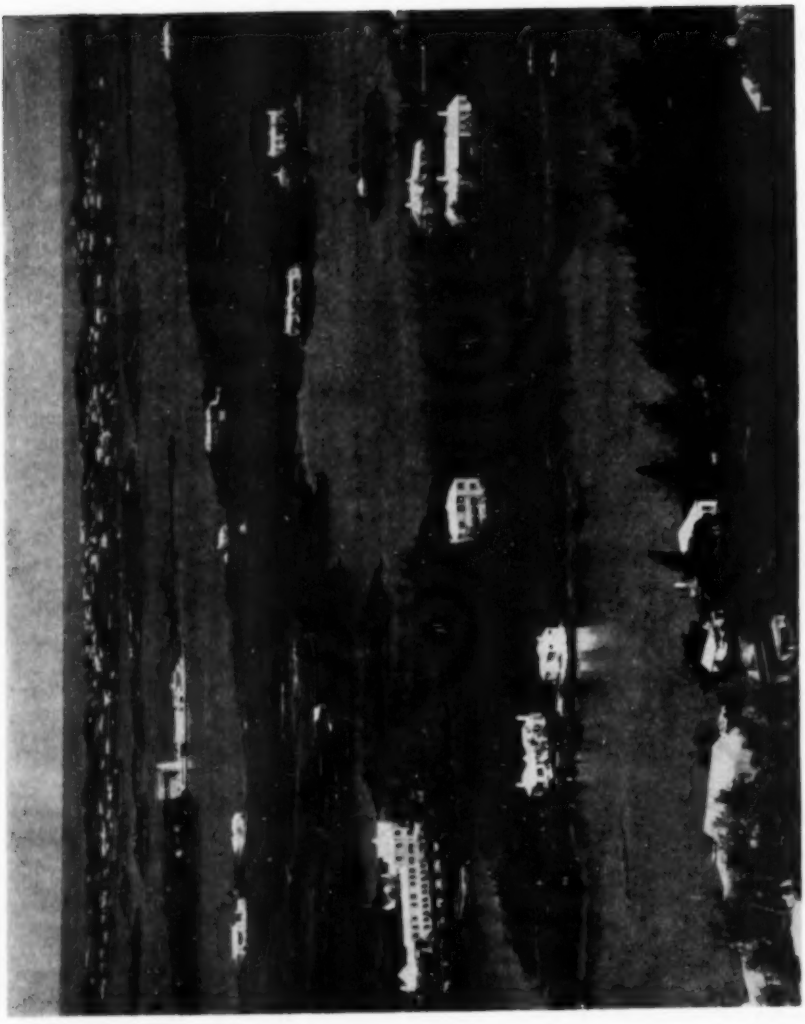
Dr. Noble P. Sherwood, F.A.C.P., Lawrence, Kans., Chairman of the Department of Bacteriology at the University of Kansas School of Medicine from 1917 to 1948, has recently become Professor Emeritus of Bacteriology. The Bacteriology Club of the University honored Dr. Sherwood at a dinner and has had his portrait placed in Snow Hall.

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The late Dr. James M. Anders, M.A.C.P., Philadelphia, has bequeathed $50,000 to the University of Pennsylvania Graduate School of Medicine to establish the James M. Anders Foundation, the sum to be added to the endowment fund of the Medico-Chirurgical College and Hospital, Graduate School of Medicine. Dr. Anders, who died Aug. 29, 1936, had left his estate in trust for his wife, and her death last February terminated the trust fund.

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Dr. Joseph F. Linsman, F.A.C.P., Beverly Hills, California, has been elected secretary of The Los Angeles Radiological Society for 1953. Dr. Wybren Heimstra, F.A.C.P., Los Angeles, California, is chairman of the executive committee of this society.



A Bermuda landscape.

## POST-CONVENTION CRUISE AFTER ATLANTIC CITY TO BERMUDA

Following three of our previous Annual Sessions held on the Atlantic Seaboard, Post-Convention Cruises have been conducted to Bermuda with great satisfaction to those who participated. Many members have inquired if the College will provide some special feature after the Thirty-Fourth Annual Session, Atlantic City, April 13–17, 1953, and we and the College have concluded to repeat the Bermuda Cruise under Mr. Leon V. Arnold, 36 Washington Square, W., New York 11, N. Y., who conducted so satisfactorily the Cruises in the past.

A doctor in Salt Lake City recently said, "Most professional meetings are crowded and only a portion can be attended. Also when away from home an extension is needed to make the trip worthwhile educationally or financially. I'm much in favor of such trips." It is an interesting fact the membership of each former cruise has represented all sections of the country.

Most of the Fellows attending the Annual Meeting from the West, North, and South will probably visit New York before returning home. New York is only three hours from Atlantic City. This offers the advantage of Friday evening in New York for the theatre, a long sleep on Saturday morning and a leisurely departure after lunch, or will it be brunch, for the ship.

The Cruise Schedule is restful and carries the additional advantage of a Scientific Forum.

Apr.

18 Sail from New York at 3:00 p.m. on the beautiful "Queen of Bermuda." The famous Bays and Skyline. Tea and Dancing.

19 The Gulf Stream, loafing in your deck chair. Forum discussions, Movies, and other entertainment.

20 Morning cruise along the charming North Shore of Bermuda and into Hamilton Harbor, one of the loveliest in the world. Ashore at 9:00 a.m.

20 Hotel Princess. Opportunity for unusual sightseeing trips to St. George,
21 around Harrington Sound to Somerset, and through Fairyland; Visits to the
22 spectacular Caves, Devil's Hole, Perfume Factory, Aquarium, and Sea Garden; Shop, Golf, or what will you?

22 Plenty of time today for last minute purchases or drives. Leave Hamilton at 3:00 p.m.

23 Again in the Gulf Stream. Forum discussions, Movies, Dancing, Fun.

24 9:00 a.m. Arrive New York. Train or plane reservations may be safely made for noon or later.

The inclusive price begins with a low of $187.55 and ranges up gradually depending on the type of room selected on the ship. The prices cover room with private bath, all privileges, and meals on the "Queen of Bermuda"; Hotel Princess with delightful room, twin beds, private bath, all privileges, and meals except for lunch on April 22 for your convenience; Federal and Bermuda taxes. A real package.

It is tentatively planned to have a Scientific Forum consisting of motion pictures on timely subjects in the field of Internal Medicine on shipboard. Details of the exact program will be published later. Such a scientific program makes the Cruise an integral part of the Annual Session and should qualify the expenses of those who participate in the program as deductible on their Income Returns.

Write now to Leon V. Arnold, 36 Washington Square, West, New York 11, N. Y. He will give you a plan of the ship, rates, full cruise information and answer your cruise questions. Many will remember him very pleasantly for he has coöperated with the College on numerous tours and has been in charge of all the previous Bermuda cruises.

## *OBITUARIES*

### DR. WALTER ARTHUR BASTEDO

Dr. Walter Arthur Bastedo, F.A.C.P., who had a distinguished career in medicine in New York City, died on July 20, 1952, of a cerebral vascular accident. He was born on March 8, 1873, in New Market, Ontario, Canada. He received his degree of Ph.G. from the New York College of Pharmacy, and his M.D. degree from the Columbia University College of Physicians and Surgeons in 1899 and a Ph.M. (Honorary) from the Philadelphia College of Pharmacy and an Sc.D. (Honorary) from Columbia University.

Dr. Bastedo served as Instructor in Pharmacology at the Cornell University Medical School from 1899 to 1901 and as Instructor in Pharmacology and Therapeutics, Associate in Pharmacology, and Assistant Professor of Clinical Medicine at Columbia University College of Physicians and Surgeons. He also served on the Attending Staff, finally becoming Attending and Consultant Physician, at the St. Luke's Hospital during the years of 1899 to 1927. He was Chief of Clinic in Gastroenterology at the Columbia University Vanderbilt Clinic from 1902 to 1908. He was Attending Physician at the City Hospital from 1913 to 1919 and Consulting Physician at the St. Vincent's and Staten Island Hospitals.

Dr. Bastedo served as an active member of the Committee and finally as President and later as Chairman of the Board of Trustees of the U. S. Pharmacopoeia. He was Chairman of the Section on Pharmacy and Therapeutics of the American Medical Association in 1919; President of the New York (1921–22) and American (1919) Gastro-enterological Associations; member of the Advisory Council of the New York Board of Health (1915–19); member of the Committee on Essential Drugs of the National Research Council; Honorary Associate of the American Proctologic Society, and a member of the New York Pathological Society. He became a Fellow of the American College of Physicians in 1924.

Dr. Bastedo's contribution to the field of pharmacology in the raising of the standards of pharmacy and the use of drugs in medical practice is a monumental one. Many physicians in practice today are deeply indebted to Dr. Bastedo for these contributions and for his friendliness and advice during these past years. It is with sorrow that these friends record his passing.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

### LIEUTENANT COLONEL CLARENCE RALPH BELL

Lieutenant Colonel Clarence Ralph Bell (MC), USA (Retired), F.A.C.P., died October 22, 1952, of a cerebral embolism. Born in Antrim, Ohio, August 16, 1883, Colonel Bell attended Illinois College and received his M.D. degree from St. Louis University School of Medicine in 1904.

Prior to attending the Army Medical School in Washington, D. C., in 1912, where he was commissioned on May 25, 1913, Colonel Bell had interned at St. Elizabeths Hospital in Washington and had served as Physician at the Peoria and Elgin (Illinois) State Hospitals.

During his twenty-year career in the Army, Colonel Bell's specialty was neuropsychiatry, and he had been Medical Officer in Charge of the Neuropsychiatric Service of the Post Hospitals at Fort Sam Houston and Schofield Barracks and at the Department Hospital, Honolulu, Hawaii. Colonel Bell also served in the Neuropsychiatric Section of the Walter Reed Army Hospital, and from 1920–22 he was the Neuropsychiatric Examiner of Recruits at Fort Slocum. In Manila Colonel Bell was formerly Medical Officer in Charge of Medical Service at the Sternberg General

Hospital. He retired from active duty in 1934 because of disease of the coronary arteries and severe arterial hypertension.

Colonel Bell had been a Fellow of the American College of Physicians since 1928 and was a member of the American Medical Association and the Association of Military Surgeons.

## DR. DAVID STANLEY LIKELY

Dr. David Stanley Likely, F.A.C.P., who practiced for many years in New York City, died on September 11, 1952, of carcinomatosis. Dr. Likely was born in St. John, New Brunswick, Canada, on July 14, 1881. He received the degree of A.B. from Mt. Allison University in 1901 and the degrees of M.D. and C.M. from McGill University Faculty of Medicine in 1905. He continued postgraduate studies in Munich and at the New York Postgraduate Medical School and Hospital.

Dr. Likely interned at the City Hospital from 1905 to 1908. He became Associate and finally Physician and Consultant to that hospital. He served as Attending Physician at the Vanderbilt Clinic from 1912 to 1916, as Attending Physician to the Children's Clinic of the New York Hospital from 1908 to 1912. He was Assistant Attending Physician and Chief of the Clinic, Instructor and Associate Professor of Medicine at the New York Postgraduate Medical School and Hospital. He also was Assistant Professor and later Professor of Clinical Medicine at the New York Medical College.

Dr. Likely was a Major in the United States Public Health Service (Reserve, Inactive, 1942–1946). He was a member of the New York County and State Medical Societies, the New York Academy of Medicine, and the American Medical Association. He was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1930. He was also a member of Phi Delta Theta and Alpha Mu Pi Omega fraternities.

It is with sincere regret that Dr. Likely's many friends and confreres record his passing at this time.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

## DR. VICTOR WARDLO VYVIAN McCORMACK

Dr. Victor Wardlo Vyvian McCormack (Associate) died suddenly at his home in Toronto on August 30, 1952. Born in Vivian, Ontario, in 1883, the son of Alexander and Martha McCormack, he was graduated in medicine from the University of Toronto Faculty of Medicine in 1908. He then served an internship at the Peter Bent Brigham Hospital in Boston, and practiced in Toronto for more than forty years. For many years he had limited his practice to family practice and to internal medicine.

Dr. McCormack served for three years in Canada in the Canadian Army Medical Corps during the First World War. He was a member of the Academy of Medicine of Toronto, the Ontario and the Canadian Medical Associations. He had been an Associate of the American College of Physicians since 1927.

His first wife, mother of his two sons, died in 1946. In 1948 he married Countess Terri du Moulin, who survives him.

RAY F. FARQUHARSON, M.D., F.A.C.P.,
Governor for Ontario

## DR. EUGENE EDMUND MURPHEY

With the passing of Dr. Eugene Edmund Murphey, F.A.C.P., on April 13, 1952, the American College of Physicians lost one of its most distinguished and versatile

members. Born in Augusta, Georgia, November 1, 1875, he lived and died in the same house to which his parents moved him in early infancy.

After graduating from the Academy of Richmond County in 1891, he attended the University of Georgia, where he was graduated from the Medical Department in 1898. His interest in medical education began early, and he became Clinical Professor of Medicine of the Medical College of Georgia in 1908 and then Professor of Medicine in 1912. In addition to his teaching activities, he was intensely interested in public health and organized medicine. Efforts in these directions culminated in his holding the position of President of the Richmond County Board of Health and Commissioner of Health from 1908 to 1933. In 1917, he was elected President of the Medical Association of Georgia.

With the outbreak of World War I, Dr. Murphey was commissioned a Major in the Army Medical Corps and served as Chief of the Medical Service, Base Hospital, Camp Gordon, Georgia. He also participated in the organization of a Medical Reserve in the State of Georgia and was a member of the Council of National Defense.

In 1920 he became a Fellow of The American College of Physicians, and throughout the remainder of his professional career he was an enthusiastic attendant at the scientific sessions of the College and a contributor to its publication.

In 1932 he suffered the loss of a leg due to thrombo-angiitis obliterans, but this did not serve to dampen his interest and enthusiasm in medical practice and teaching. It was a source of great inspiration to his contemporaries to see him at medical meetings in a wheel chair, usually more cheerful and enthusiastic than those about him.

Because of his physical condition, Dr. Murphey retired from the practice of medicine in 1934. This, however, did not mark the end of his productive career. His inexhaustible energies then flared in the direction of his cultural interests, and this resulted in the publication of a book entitled "Observations on the Bird Life of the Middle Savannah Valley," in 1938. His interest in ornithology had been life-long, and in 1933 he became Honorary Curator of Ornithology at the Charleston (S. C.) Museum.

His ability as a poet was another of his virtues. This resulted in the publication, in 1939, of a collection of short poems, titled "Wings at Dusk."

Dr. Murphey was a member of the Chi Phi, Phi Rho Sigma and Alpha Omega Alpha fraternities.

Dr. Murphey's family, his innumerable friends and his medical contemporaries count his passing as the irreplaceable loss of a great physician, teacher, poet and ornithologist. He contributed much to those who were so fortunate as to be touched by his inspiring personality.

CARTER SMITH, M.D., F.A.C.P.,
Governor for Georgia

## DR. ROBERT DICKSON ROACH

Robert Dickson Roach, M.D., F.A.C.P., was born in Tatamagouche, Nova Scotia, on November 26, 1898, son of Dr. E. D. Roach, who in that day was family physician and friend to the community.

He was graduated with M.D. and C.M. degrees from McGill University Faculty of Medicine in 1925, and his earliest practice was in Dorchester, New Brunswick. This was followed by postgraduate training in the specialty of medicine in England, where he obtained his degree of M.R.C.P. (London) in 1932. Returning to New Brunswick the same year, he settled in the city of Moncton to practice his specialty and to become Senior Physician and Cardiologist to the Moncton City Hospital.

In 1938 he was granted Fellowship in the American College of Physicians, and in 1949 received the Fellowship of the Royal College of Physicians (Canada). He continued practice in Moncton until the time of his last protracted illness and death on July 28, 1952.

Dr. Roach was a man of broad interests and outstanding personality, and was generally acknowledged as a leading practitioner and sound consultant in his province. Of impeccable ethics and well balanced judgment, he also took an active part in medical administrative affairs, and at the time of his death he was President of the New Brunswick Medical Society.

A quotation from a eulogy recently delivered by Dr. Charles L. Gass, F.A.C.P., a lifelong friend of Dr. Roach, expresses the general tribute to him:

> "As a man, among Dr. Roach's many qualities, two were outstanding. He had an acute appreciation of human values and a rare sense of humor, which combination allowed him to look out on the passing show of life with equanimity. He was never ruffled. He never showed disappointment or anger, although he experienced both.
>
> "As a physician, he had a first-class intellect, and his work was marked by a patient and unhurried thoroughness that is difficult to maintain in these hurried days. All these qualities made him a beloved physician to his patients, for he combined in a rare degree the art and science of medicine. He stood high in the esteem of all who knew him. He has undoubtedly left his mark on New Brunswick medicine, and our profession is the better for his life and work among us."

A. B. WALTER, M.D., F.A.C.P.,
Governor for the Maritime Provinces

## DR. LAWRENCE C. TOWNE

Dr. Lawrence Chatfield Towne, F.A.C.P., was born in Geneva, Michigan, in 1884. He attended both the University of Michigan and the University of Michigan Medical School before receiving his M.D. degree from the Northwestern University Medical School in 1909. He later pursued postgraduate studies at the Harvard Medical School.

Following graduation from Northwestern, he became a member of the staff of Toledo Hospital for one year, and in 1915 joined the staff of the Edward W. Sparrow Hospital in Lansing, Michigan, becoming a Chief of the Medical Services in 1949. Since 1920 Dr. Towne had also been a member of the staff of St. Lawrence Hospital.

He was a former Secretary of the Ingham County Medical Society, a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1922.

One of Dr. Towne's associates has stated, "I cannot overemphasize the great service that he rendered the Edward W. Sparrow Hospital over a long period of years. He served as Chief of Medicine for years, and a few years as Chief of Staff. He was one of the few deserving major credit for advances in the medical standards of the hospital. He had a host of friends, and his patients literally worshipped him."

Dr. Towne died from coronary arteriosclerosis with acute cardiac failure on August 16, 1952.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

## DR. HENRY PULTENEY WRIGHT

Dr. Henry Pulteney Wright, F.A.C.P., of Montreal, died after a short illness in the Royal Victoria Hospital, Montreal, on January 27, 1952.

Dr. Wright was born in Ottawa in 1888, obtained his A.B. degree from the University of Bishop's College in 1909, and graduated from the McGill University Faculty of Medicine in 1914. After graduation he was an interne in the Montreal General Hospital until his enlistment in the Royal Canadian Army Medical Corps in 1914 for overseas service in the First World War. After four years of service, he was discharged in 1918 with the rank of Major.

After the war, Dr. Wright studied in London, Berlin and Copenhagen. Returning to Montreal, he took up the practice of pediatrics, serving as Physician, Children's Memorial Hospital; Physician, Montreal Foundling and Baby Hospital, and Pediatrician at the Royal Victoria Hospital. At the same time he was appointed to the teaching staff of McGill University, serving as Demonstrator, Lecturer, and later as Assistant Professor of Medicine.

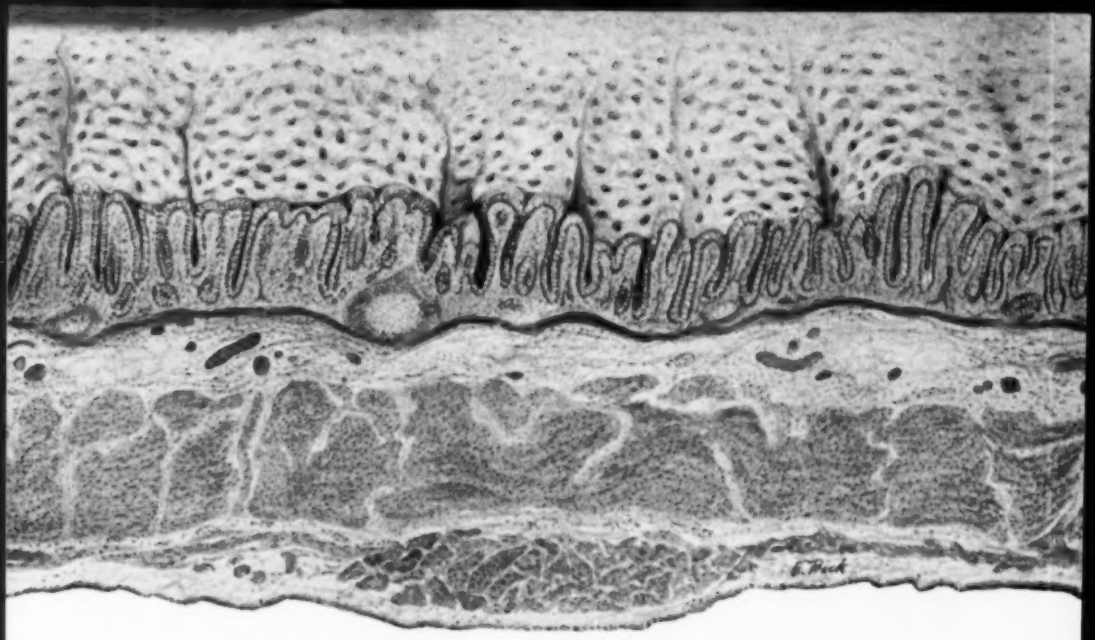
Later in life Dr. Wright became actively interested in the problem of arthritis. He organized an arthritis clinic in both the Royal Victoria and the Queen Mary Veterans Hospitals, served as President of the Canadian Rheumatism Society, and was actively associated with the Quebec Division of the Canadian Arthritis and Rheumatism Society, being a director of the latter organization at death.

Dr. Wright will be remembered for his drive and capacity to initiate new enterprises. At the Royal Victoria Hospital his efforts established a Postgraduate Board for the promotion of postgraduate medical education, which has continued to function successfully. He also founded the Osler Reporting Society in Montreal.

He was a Fellow of the Royal College of Physicians (Canada); a Fellow of the American College of Physicians since 1931, and a Fellow of the American Academy of Pediatrics. He was a member of the Canadian Medical Association, the Montreal Medico-Chirurgical Society, American Rheumatism Association, Canadian Society for the Study of Diseases of Children, and the Osler Reporting Society. His major medical contributions were in the fields of childhood tuberculosis and arthritis.

Dr. Wright will always be remembered for his lovable personality, companionship and varied interests. He had a fertile mind with the necessary drive to accomplish much.

EDWARD H. MASON, M.D., F.A.C.P.



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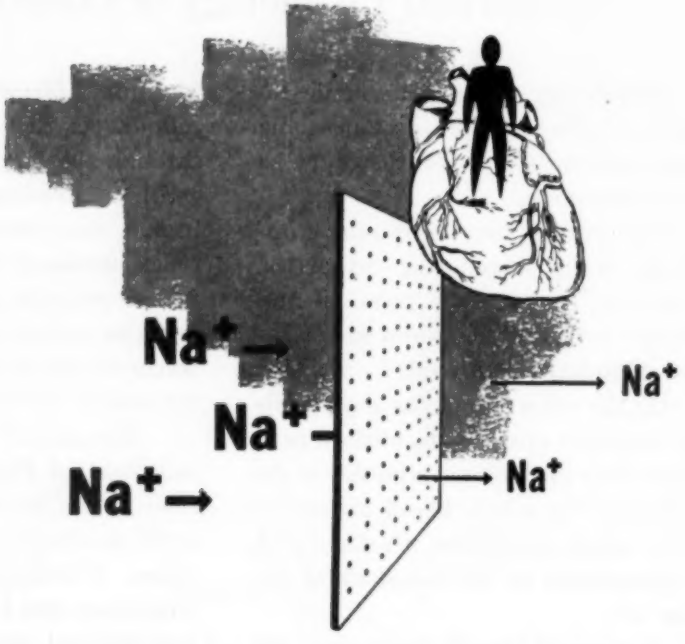
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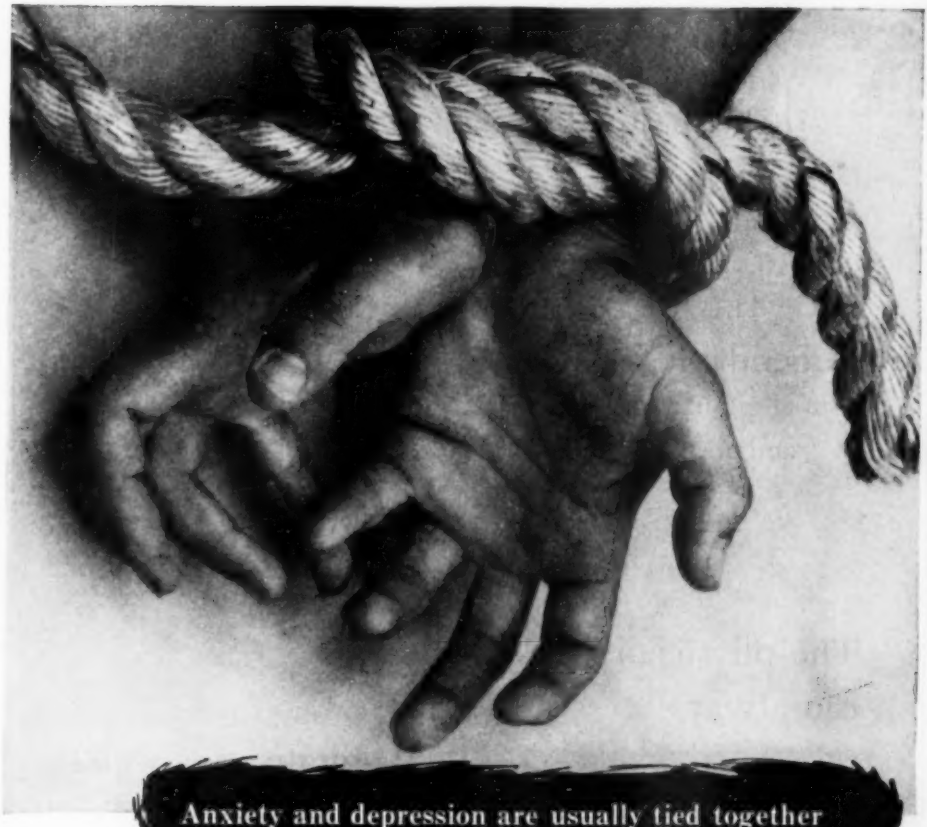



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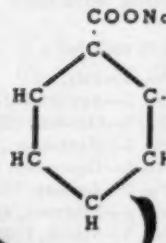
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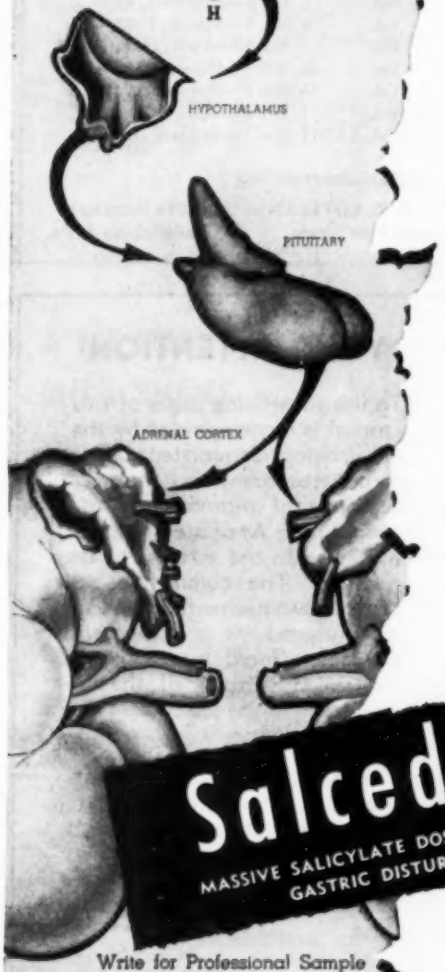
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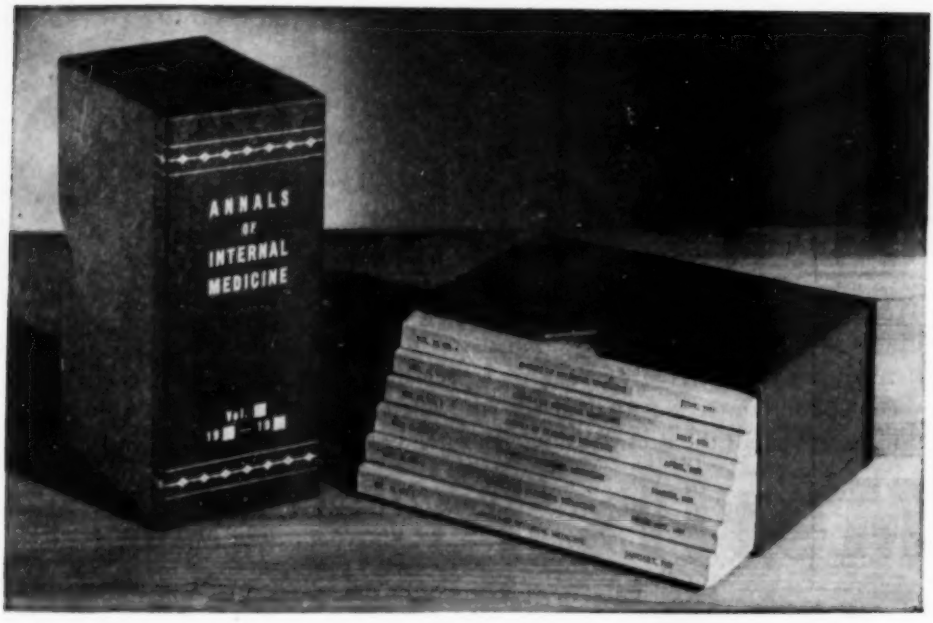
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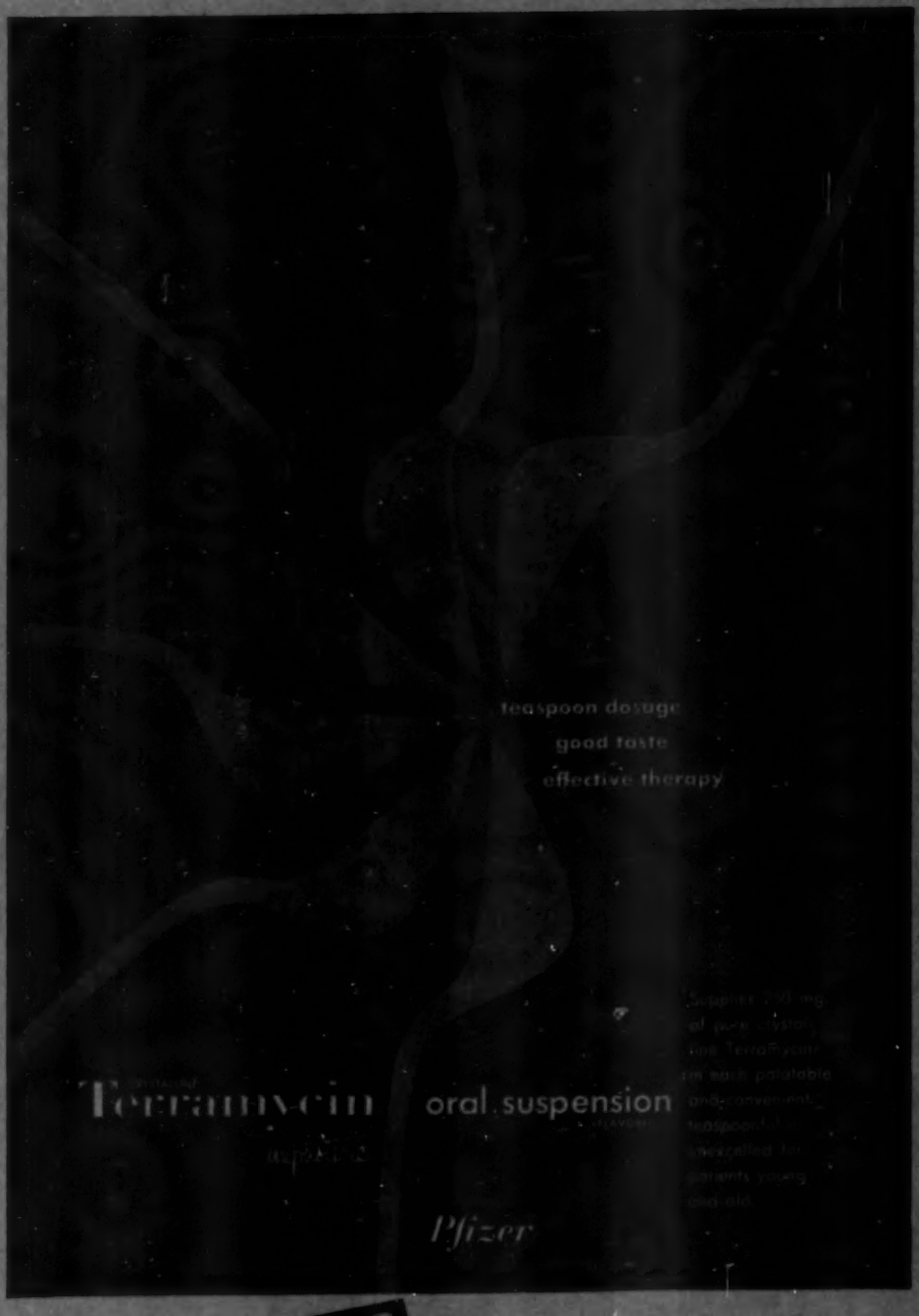
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